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A CONCISE APPLIED PHARMACOLOGY AND THERAPEUTICS

A CONCISE APPLIED PHARMACOLOGY AND THERAPEUTICS

OF THE MORE IMPORTANT DRUGS, TOGETHER WITH AN INTRODUCTION TO THE ART OF PRESCRIBING

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THIRD EDITION

LONDON
LEONARD HILL LIMITED, 17 STRATFORD PLACE, W.1
1949

FIRST EDITION DECEMBER 1937
SECOND EDITION JULY 1944
REPRINTED SEPTEMBER 1946
THIRD EDITION 1949

BOOK
PRODUCTION
WAR ECONOMY
STANDARD

This Book is produced in complete conformity with the
Authorized Economy Standards

PRINTED IN GREAT BRITAIN BY NEILL AND CO. LTD., EDINBURGH

FOREWORD

The invitation to contribute a foreword to any book is a rare compliment of which no man can fail to be sensible. It is a privilege which connotes not only a personal acquaintance with the author, but the implication of special knowledge of the subject. Whilst I am humbly conscious of failing in authority, in respect of the former qualification I am happily circumstanced. The Dean of a Medical School has vested interests. His prime consideration is the education of his students, whose advancement he endeavours jealously to maintain in the hurly-burly of hospital activity, where the care of the sick has to run *pari passu* with undergraduate instruction. And although there can be little doubt that reciprocal advantage is in this way ensured, the achievement is not without difficulty. From close association with the authors of this work, in the wards and out-patient department and the Medical School, activities in which their services have been invaluable, I was entitled to anticipate with confidence the fruitful co-operation of a pharmacist and a physician. And it may be added that in this instance the pharmacist is one with a distinctly clinical acumen, and the physician a clinician with exceptional pharmacological experience as a teacher.

The work is planned for the student, who will find it sufficiently comprehensive for all his examinations both in academic and applied pharmacology, and yet not so elaborate as to prejudice him when time and energy are so precious in his overburdened curriculum; and he will certainly see the importance of its application at two distinct stages of his career.

I am personally gratified that this useful book emanates from the Hospital and Medical School with which I am so intimately concerned.

ADOLPHE ABRAHAMS.

INTRODUCTION

This volume represents an attempt to present concisely, but in sufficient detail, the pharmacology of the more important drugs used in the British Commonwealth and the United States of America.

The requirements of the student of experimental pharmacology are already fully covered by the larger text-books available, and this volume seeks only to discuss the action of drugs in relation to practical therapeutic considerations.

It is hoped that the specimen prescriptions included will stimulate the student to experiment in the construction of original formulas; the more important galenical preparations, which are mentioned, should also facilitate prescribing.

For the convenience of students preparing for examinations, some sections are set in smaller type; in the main these relate to less important drugs of which no detailed study is required.

The arrangement adopted for the subject-matter has, in places, necessitated the grouping together of drugs somewhat heterogeneous in character. Pharmacology is, however, a notoriously difficult subject to arrange, and it is hoped that the index will provide all facility of reference. In the case of a few drugs which do not properly belong to any of the main divisions adopted for classification, a description has been added as a subsidiary monograph to some other drug with which they may possess some sort of affinity.

As far as practicable without destroying the utility of the book, reference to proprietary medical products has been minimised. In certain instances where well-known proprietaries are identical with, or similar to, the drug under discussion, the proprietary name has been added. In all these cases the name is commenced with a capital letter, printed in italics and designated with an asterisk. These measures are taken because the writers feel that although a prescriber may, for some reason, desire a proprietary brand, it is in the highest degree confusing and undesirable that proprietary names should be used indiscriminately as interchangeable with the chemical and pharmaceutical designations.

Finally the authors wish to extend their grateful acknowledgments to Dr. Adolphe Abrahams for kindly contributing a foreword to the volume, and to Messrs. S. A. Taylor, B.Pharm., Ph.C., and E. W. Simpson, M.P.S., for many helpful suggestions, and assistance in preparing the manuscript for the press.

F. G. HOBART.
G. MELTON.

London, 1937.

PREFACE TO THE SECOND EDITION

THE reception accorded to the first edition of this volume indicates that despite, or perhaps because of, the vast wealth of literature dealing with pharmacology, there exists a need for a concise exposition of modern knowledge and theory of the subject, especially in its relation to clinical practice. In this edition greatly increased attention has accordingly been given to those therapeutic considerations which the clinician is most likely to appreciate. This policy, together with the need for extensive references to the many new and important drugs which have come into use within the past few years, has necessitated an almost complete rewriting of the text, and the opportunity has been taken, also, to effect a slight modification of the title which will make it more accurately descriptive. In order to incorporate much new matter without undue enlargement of the volume, references which appeared in the first edition to drugs of minor general importance have been minimised or excluded. As in the first edition, the classification adopted is essentially pharmacological, but considerable rearrangement has been made with the purpose of improving facility of reference. Attention must again be drawn to the fact that some drugs do not fit conveniently into a scheme of pharmacological classification of practicable dimensions, and in a few cases (*e.g.* Chrysarobin) a description of these has been attached as a sub-monograph to a drug with which they have some chemical relationship.

Although produced in time of war, the authors have not deemed it necessary to refer in the text to temporary shortages of supply of certain drugs, or to recommend substitutes. These matters are adequately and more appropriately covered by *ad hoc* publications. In this regard reference is directed to that handy and excellent pamphlet issued by the Medical Research Council[1] and to the modified formulas which have been adopted for preparations of the Pharmacopœia and the British Pharmaceutical Codex.

The authors' grateful thanks are due to the many friends who have made helpful suggestions regarding the text, and to the publishers, Messrs Leonard Hill Ltd., without whose close co-operation the difficulties attendant upon new publications in these times would have been insurmountable.

---

[1] *Economy in the Use of Drugs in War-Time*, published by H.M. Stationery Office, price 3d.

1944.

PREFACE TO THE THIRD EDITION

The continued and increasing demand for this work leads the authors to the flattering conclusion that it has proved a useful handbook to both students and practitioners.

Considerable pruning of the monographs relating to drugs of secondary importance has been necessitated to make room for the inclusion of much new matter, especially in regard to chemotherapeutic agents, hormones and vitamins, and an attempt has been made to provide sufficient detail for the intelligent clinical use of the products named.

Finally, the printing and production of this edition had so far advanced by the time of the issue of the 1948 British Pharmacopœia (September 1st) that it has not been possible to incorporate all the changes in preparations, and nomenclature introduced by the official volume.

1949.

KEY TO ABBREVIATIONS OF MANUFACTURERS' NAMES

Ab.—Abbott Laboratories.
A.F.—Anglo-French Drug. Co.
A.H.—Allen & Hanburys.
Am.—Armour.
Ba.—Bayer Products.
B.D.H.—British Drug Houses.
Be.—Bengers.
Bg.—Bengue.
Bo.—Boots.
Br.—British Organotherapy.
Bro.—Brooks & Warburton.
B.S.—British Schering.
Bu.—Bush.
B.W.—Burroughs Wellcome.
C.C.—Cavendish Chemical Co.
Ci.—Ciba.
Co.—Coates & Cooper.
C.P.—Clinical Products.
Cr.—Crookes Laboratories.
De.—Denvers Chemical Co.
D.F.—Duncan & Flockhart.
E.L.—Eli Lilly.
En.—Endocrines, Spicer.
Ev.—Evans Medical Products.
Ex.—Ex-Lax Ltd.
F.J.—Fassett & Johnson Ltd.
Fe.—Ferris.
Ge.—Genatosan.
Gl.—Glaxo.
He.—Hewlett & Sons, Ltd.
Ho.—Howard & Sons.
H.P.—Herts Pharmaceuticals.
I.C.—Imperial Chemicals.
Jo.—Johnson & Sons.
Ka.—Kaylene Ltd.
Ki.—Kirby.
Kn.—Knoll.
Le.—Lederle
Li.—Lilly.
Ly.—Lysol, Ltd.
Ma.—Martindale.
Mac.—Macfarlane.
M.B. — Pharmaceutical Specialties (May & Baker) Ltd.
M.J.—Menley & James.
M.L.—Monsol Ltd.
M.M.P.—Moore Medicinal Products.
M.P.—Modern Pharmaceuticals.
Nap.—Napp.
Nat.—Laboratory Nativelle.
No.—Norgine.
Or.—Organon Laboratories.
Op.—Oppenheimer, Son & Co. Ltd.
Ox.—Oxo.
P.B.—Paines & Byrne.
P.D.—Parke Davis.
P.M.—Pharmaceutical Mfg. Co.
P.P.—Pharmaceutical Products.
R.—Roche Products.
Ri.—Richter Ltd.
Re.—Reckitt & Sons.
Ro.—Roberts.
Rou.—Roussell.
Sa.—Sandoz Products.
Sac.—Saccharine Corporation.
Sc.—Scott & Bowne.
Sch.—Schering.
S.D.—Sharp & Dohme.
S.M.—Savory & Moore.
So.—Southall Bros. & Barclay.
Sq.—Squibbs.
Ste.—Stemco.
T.P.—Therapeutic Products.
Tr.—Trufood.
Vit.—Vitamins Ltd.
Wan.—Wander.
Wh.—Whiffen.
W.J.—Wilcox & Jozeau.
W.P.—Warwick Pharmaceuticals.
W.W.—William Warner & Co. Ltd.
Wy.—Wyeths.
Wyn.—Wynthrop.
Zi.—Zimmermann.

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DRUG INCOMPATIBILITY

Pharmacological Incompatibility.—By this is meant the concurrent administration of drugs producing opposite effects—*e.g.* chloral hydrate and strychnine.

Physical Incompatibility means that the substances cannot be successfully manipulated together—*e.g.* 10 oz. of chalk cannot be suspended in 1 fl. oz. of water. Sometimes physical incompatibility can be overcome—*e.g.* oil and water do not mix unless an emulgent be added.

Chemical Incompatibility.—This connotes that when the substances are mixed, chemical reaction *undesired* by the prescriber takes place. The chief chemical incompatibilities are:

Acids (and acid salts)	Alkalis. Nitrites. Salicylates.
Alkalis	Alkaloids.[1] Ionised iron. The salts of mercury and of the heavy metals generally.
Alkaloids	Tannic acid.[1] Bromides.[1] Iodides.[1]
Bismuth salicylate	Alkalis. Acids.
Calcium (soluble salts of)	Alkalis.
Ionised iron	Tannic acid. Salicylates. Iodides.
Silver salts	Organic matter. Tannic Acid. Chlorides.

---

[1] Unless well diluted.

SOME DEFINITIONS

Drugs are substances used to augment, decrease or modify the functioning of an organ or a tissue; they are obtained from the three kingdoms of Nature. The study of the chemical and physical properties of organised drugs, and of their sources, is termed **pharmacognosy.** The various operations by which crude drugs are prepared and standardised for medicinal use comprise **pharmacy;** while **pharmacology** treats of the action of drugs upon the organism. The term **pharmaceutics** is used to describe a sphere of study embracing these three main subjects together with various ancillary subjects including general chemistry, physics, physiology, zoology and botany. Finally, drug **therapeutics** deals with the application of pharmacology to the treatment of disease.

In prescribing medicaments it is customary to use a conventionalised Latin terminology which has the infinite advantage of lending itself to crisp and clear abbreviation, and of being comprehensible in all civilised countries. The system of weights and measures still very largely used by prescribers throughout the British Commonwealth of Nations and in the United States of America, namely the Apothecaries' system, has certain disadvantages, but it is closely related to everyday measures, and continues as the most favoured medium despite the attempts which have been made to persuade the medical profession to adopt the metric system. The latter system has its advantages, but it seems highly undesirable that medical students should try to obtain some command of posology on *two* systems.

Accordingly, this book expresses the majority of doses and illustrates prescribing on the Apothecaries' system. **That it has not been found practicable to be wholly consistent in this matter is due to the fact that prescribers are in the early stages of a very slow transition from the Apothecaries' to the metric system,** and in the case of drugs which it is now customary to prepare and prescribe in metric quantities, dosage is expressed upon that system. It is hardly necessary to stress how great is the need for caution while two such widely different systems for expressing dosage are in simultaneous employment.

In the Apothecaries' system the smallest whole unit of weight is the grain (*granum*), which is $\frac{1}{7000}$ part of the Imperial pound (lb.); quantities of less than 1 grain are expressed as vulgar fractions, an inconsistency which custom has regularised. A common exception to this rule, however, is that one-half (*semisse*) is generally symbolised by a double ess—viz. ss, and often the first ess is written as the otherwise obsolete "long ess" so the symbol appears thus: ſs.

Other quantities are expressed by symbols and Roman numerals:

gr. xx = ℈i, one scruple.
℈iii = ʒi, one drachm.
ʒviii = ℥i, one ounce.

The smallest whole unit of volume is the minim (*minimum*), which is *not* the same as a drop. Drops are variable in volume according to viscosity, etc., but the volume of the minim is invariable. Nor is there any simple mathematical relationship between grains and minims such as exists between grammes and millilitres. On the Apothecaries' system a 1% solution of a solid in a liquid contains 1 grain in approximately 110 minims. Measures of volume are:

♏lx =fl. ʒi, one fluid drachm.
fl. ʒviii=fl. ℥i, one fluid ounce.
fl. ℥xx=Oi (*octarius*), a pint.

It is customary to omit the fl. (*fluidus, -a -um*) in front of the symbol because of the general convention that liquids are to be measured by volume unless there are specific directions to the contrary.

The conventional relationship between the above measures of volume and domestic measures are as follows:—

fl. ʒi =a teaspoonful.
fl. ʒii =a dessertspoonful.
fl. ʒiv (or ℥ſs.)=a tablespoonful.
fl. ℥ii =a wineglassful.
fl. ℥x =a tumblerful.

The doses given are mainly those of the British Pharmacopœia, the British Pharmaceutical Codex and the Pharmacopœia of the United States. The official maximal dosage is not binding upon a prescriber, but **pharmacists are under legal obligation to query doses in excess of the maxima unless they are specially marked and initialled to indicate clear intent.**

THE STANDARDISATION OF DRUGS AND THEIR PREPARATIONS

THE pharmacological action of organised drugs is due not, of course, to the basic tissues of which they are composed, but to specific chemical substances elaborated during the life of the animal or plant from which the drug originally was derived. These chemical entities may have served some vital physiological purpose, have resulted from pathological influence or be mere by-products of metabolism. In any case, for climatic and nutritional reasons, there is wide variation in content of these bodies in the parent tissue. In order, therefore, to ensure uniformity, it is necessary for all important drugs to be of standardised potency in the forms in which they are prepared for medication. The preparations, too, must be of such a nature that reasonable stability is ensured under appropriate conditions of storage.

Where practicable, standardisation is based upon chemical assay of the most important active principle of the drug, *e.g.* morphine in opium or strychnine in nux vomica. In general, chemical assay is extremely accurate, not unduly tedious and relatively economical. In the case of a number of important drugs, however, no reliable chemical process for the determination of potency has been devised, and in these circumstances biological standardisation upon groups of living animals, or upon freshly isolated animal tissue, is perforce adopted. These biological methods are by no means ideal. They are often tedious and expensive to carry out, and a margin of error of 20% in either direction is not uncommon. The following brief summary of the biological processes adopted by the British Pharmacopœia will serve to convey a general idea of the methods in use. All the official assays are made in parallel with material of known potency, the ultimate standard preparations for Great Britain and Northern Ireland being conserved under suitable conditions of storage by the National Institute for Medical Research of London.

Digitalis (and Strophanthus).

A determination is made of the average lethal dose on **frogs** in comparison with that of the standard preparation.

Alternatively

using **cats** or **guinea-pigs,** an aqueous extract is injected slowly into the veins of anæsthetised animals (respiration being maintained artificially) until the heart is stopped. The quantity required is compared with the standard preparation.

Insulin.

The potency of insulin is determined by comparing samples with the standard preparation, in causing fall of blood-sugar level in groups of rabbits or, *alternatively,* convulsions in mice.

The Standardisation of Drugs and their Preparations

Neoarsphenamine (and Sulpharsphenamine).

These drugs are tested:

(*a*) for undue toxicity to rats or mice in comparison with the standard preparation. Neoarsphenamine is injected intravenously, and Sulpharsphenamine subcutaneously;

(*b*) for therapeutic activity in parallel with the standard preparation on rats or mice infected with trypanosomes.

Posterior-Pituitary Extract.

The activity of the sample is compared with that of the standard preparation in causing contraction of the isolated uterus of the guinea-pig suspended in a Ringer-Locke solution.

Vitamin D.

The anti-rachitic potency of vitamin D preparations is compared with the standard preparation by administering them to mice previously fed on a rachitogenic diet, and later determining, by means of X-ray photographs or by examining the distal ends of the ulnæ and radii after staining, the extent to which rickets has been cured.

Penicillin.

The B.P. requires the potency of penicillin to be determined by comparing the quantity which inhibits the growth of a sensitive strain of *staph. aureus* with the quantity of the standard which produces the same inhibition. This can be done by: (1) The Serial Dilution Method, in which the inhibition of growth produced by varying dilutions of penicillin in a broth culture of *staph. aureus* is noted; (2) The Cylinder Plate Method. Here penicillin is placed in bottomless cylinders which rest on agar plates seeded with *staph. aureus*. The diameter of zones of inhibition of growth produced by the drug is noted. Methods of determining the amount of penicillin in body fluids depend upon its prevention of hæmolysis when a culture of *strep. hæmolyticus* is incubated with red cells. Chemical methods of assay depend upon titration of penicilloic acids produced by inactivation with penicillinase Colorimetric methods also are available.

COLLOIDS IN MEDICINE

In view of the prominence which has been given to the medicinal uses of substances in the colloid state, the following brief account of the nature and uses of colloidal preparations may be of utility.

Solute particles in a true solution are of molecular dimensions, about 0·1 $\mu\mu$ (10^{-7} mm.), but in colloidal dispersions the dispersed phase consists of aggregates varying in size according to the method of preparation. The still minute dimensions of the aggregates, of the order of 1–100 $\mu\mu$, permits them to remain suspended indefinitely by reason of Brownian movement; a result of bombardment by the molecules of the solvent.

Exemplifying dispersed solids may be cited colloidal **sols** of both metallic and non-metallic elements, also preparations such as argentoprotein, iron and ammonium citrate, and certain dyestuffs like congo-red.

Fundamentally, ordinary emulsions constitute dispersions of liquid in liquid, and the greater the degree of dispersion the nearer these preparations approach to the orthodox conception of **emulsoids.**

In a special type of dispersion, the **gel,** the continuous phase or medium has a reticulate structure in which the dispersed phase is enmeshed; examples are agar and gelatin, also adsorbents like kaolin and magnesium trisilicate.

The preparation of elegant and effective pharmaceuticals frequently calls for judgment regarding the order or method of mixing ingredients, so that an active principle may be presented as a dispersion. **Protective colloids** such as acacia and the saponins are often utilised to facilitate such dispersion.

The especial value of metallic and other sols is doubtful when they are administered by mouth, on account of the strongly reactive nature of the gastric acid which may destroy the colloid state. There are, however, obvious exceptions. In the case of iron ammonium citrate it is essential that the colloidal state be broken down in order to facilitate absorption of iron. Where adsorption is required (*e.g.* kaolin), or where the enormously enlarged surface area presented by matter in the colloidal state increases reactivity (*e.g.* sulphur), oral medication is perfectly rational.

The factor of increased reactivity, etc., is of equal importance when the substances named and others of similar type are intended for external application. Reference will be made (see the section on the Metals) to the slow liberation of ions from ordinarily insoluble compounds in contact with tissue fluids, and it follows that the greater the degree of dispersion the more active such an insoluble compound can be regarded, since ionisation is facilitated by the increased surface for reaction to occur.

The fact that colloids do not diffuse through membranes like true solutions, invests them with especial value in depot therapy. One example of this is protamine insulin suspension.

Naturally-occurring colloids include the proteins, where the colloidal character is due to the relative magnitude of the molecules and the development of chains and cross-linkages. Further examples are saponins and other glycosides and the bile salts and soaps, which possess large polar molecules.

PROPRIETARY DRUGS AND THEIR DEFINITIONS OR NON-PROPRIETARY EQUIVALENTS

The manufacturers of the following preparations are indicated by the abbreviations in parentheses, and a key to these is provided on page ix.

Abasin (*Ba.*)—Acetyl carbromal.
Abacedin (*Nap.*)—Vitamins A, B, C, D.
Abidon (*P.D.*)—Vitamins A, B, D.
Abrodil (*Ba.*) — Moniodosulphonate compound for pyelography.
Acecoline (*A.F.*)—Acetylcholine.
Acetidine (*S.D.*)—Acetylsalicylic acid, phenacetine and caffeine.
Acetylarsan (*M.B.*) — Diethylamine acetarsol.
Acidol (*Ba.*)—Betaine hydrochloride.
Acigen (*M.B.*)—Mandelic acid preparation.
Acramine (*Gl.*)—Aminoacridine.
Adalin (*Ba.*)—Carbromal.
Adexolin (*Gl.*)—Vitamin A and D concentrate.
Adrenatol (*Ev.*)—Adrenaline solution.
Adrephine (*P.D.*) — Adrenaline and ephedrine solution.
Agarol (*W.W.*)—Emulsified mineral oil and phenolphthalein.
Agocholine (*Bg.*)—Magnesium sulphate and peptone granules.
Agotan (*Ho.*)—Cinchophen.
Alamelin (*Ba.*)—Aluminium hydroxide gel.
Alasil (*Wan.*)—Acetylsalicylic acid, colloidal aluminium hydroxide.
Albargin (*Ba.*)—Combination of silver nitrate and gelatose.
Albucid (*B.S.*)—Sulphacetamide.
Aleudrine (*W.J.*)—Isopropyl adrenaline.
Algiron (*Ev.*)—Organic iron salt.
Allonal (*R.*)—Allylisopropylbarbituric acid and amidopyrine.
Allodene (*Bu.*)—Amphetamine.
Alocol (*Wan.*)—Colloidal aluminium hydroxide.
Alophen (*P.D.*)—Compound aloin pill and phenolphthalein.
Alopon (*A.H.*)—Papaveretum, B.P.C.
Alphidine (*Op.*)—Iodine complex.
Aludrox (*Wy.*)—Colloidal aluminium hydroxide.
Ambeside (*Ri.*)—Sulphacetamide.
Ambinon (*Or.*)—Anterior pituitary hormones.
Amechol (*S.M.*) — Acetyl-β-methyl choline.
Ametox (*M.B.*) — Brand name for various thiosulphates.
Ammoket (*Bo.*)—Ammonium mandelate.
Ammitonin (*S.M.*)—Œstrone.
Amytal (*Li.*) — Isoamylethylbarbituric acid.
Anacardone (*B.D.H.*)—Nikethamide.
Anæsthesin (*Ba.*)—Benzocaine.
Anahæmin (*B.D.H.*) — Injectable liver preparation.
Ana-hepol (*A.H.*)—Liver preparation.
Analsol (*Ka.*)—Methylaspirin for local application.
Androfort (*Ri.*)—Androsterone.
Anesthone (*P.D.*)—Benzocaine.
Anethaine (*Gl.*)—Amethocaine.
Anthiomaline (*M.B.*)—Lithium antimony thiomalate.
Anthisan (*M.B.*)—Neoantergan.
Antiphlogistine (*De.*)—Kaolin poultice.
Antistin (*Ci.*) — Imidazoline antihistamine compound.
Antostab (*Bo.*)—Serum gonadotrophin.
Antoxylin (*Oxo*) — Chorionic gonadotrophin.
Antroidin (*P.D.*) — Anterior pituitary extract.
Aplona (*Co.*)—Preparation of apple pectin.
Arecan (*Ev.*)—Procaine and adrenaline solution.
Antregone (*Ab.*) — Chorionic gonadotrophin.
Antrypol (*I.C.*)—Suramin.
Antruitin (*P.D.*) — Anterior pituitary extract.
Apondon (*C.C.*)—Thyroid extract with ergot.
Arcolax (*Rou.*)—Psyllium.
Argein (*A.H.*)—Silver proteinate.
Argyrol (*F.J.*)—Mild silver proteinate.
Aristol (*Ba.*)—Thymol triodide.
Armo-Nœstrol (*Arm.*)—Dienœstrol and phenobarbitone.
Arritin (*Jo.*)—Mild silver proteinate.
Arthrytin (*M.B.*) — Calcium ortho-iodoxy-benzoate.
Ascabiol (*M.B.*) — Benzyl benzoate emulsion.
Asensitine (*D.F.*) — Procaine and adrenaline.
Aspiriodin (*Ma.*) — Acetyliodosalicylic acid.
Aspro (*As.*)—Acetylsalicylic acid.

Asthmolysin (*Zi.*) — Andrenaline and pituitrin.
A.T. 10 (*S.M.*)—Dihydrotachysterol.
Atebrin (*Ba.*) — Mepacrine hydrochloride.
Atophan (*B.S.*) — Cinchophen.
Atophanyl (*B.S.*)—Cinchophen sodium salicylate for injection.
Atoxyl (*Boe.*)—Sodium aminoarsenate.
Auro-calcium (*Ci.*) — Calcium aurothiomalate.
Aurobin (*Ri.*)—Sodium aurithiosulphate.
Avertin (*Ba.*)—Bromethol.
Avoleum (*B.D.H.*) — Vitamin A concentrate.
Azazol (*Bo.*)—Hexazole.
Azochloramid (*W.T.*) — Dichloroazodicarbonamidine.

Basergin (*Sa.*)—Ergometrine tartrate.
Bayer 205 (*Ba.*)—Suramin.
Becosyn (*R.*)—Vitamin B-complex.
Beflavit (*R.*)—Riboflavine.
Befortiss (*Vit.*)—Vitamin B-complex.
Belladenal (*Sa.*)—Belladonna alkaloids and phenobarbitone.
Bellafoline (*Sa.*)—Lævorotatory belladonna alkaloids.
Bellergal (*Sa.*)—Bellafoline, ergotamine, phenobarbitone.
Bemax (*Vit.*)—Whole wheat-germ food.
Benadon (*R.*)—Pyridoxine.
Benadryl (*P.D.*) — Complex antihistamine compound.
Benerva (*R.*)—Aneurine hydrochloride.
Benzedrine (*M.J.*)—Amphetamine.
Benzeran (*Ev.*)—Benzyl benzoate.
Beplex (*Wy.*)—Vitamin B-complex.
Berin (*Gl.*)—Aneurine hydrochloride.
Betabion (*S.M.*)—Vitamin B_1.
Betaborocaine (*B.H.D.*)—Benzamine borate.
Betalin (*E.L.*)—Vitamin B_1.
Betaxan (*Ba.*) — Aneurine hydrochloride.
B.F.I. (*S.D.*)—An antiseptic dusting powder.
Biarsamide (*M.B.*)—Bismuth tryparsamide.
Bilein (*Ab.*)—Bile salts.
Binæmon (*Or.*)—Liver extract and hog's stomach.
Bisantol (*M.B.*)—Bismuth salicylate in oil.
Bisglucol (*M.B.*)—Bismuth injection.
Bismecol (*M.B.*)—Bismuth ethyl comphorate.
Bismostab (*Bo.*)—Bismuth injection.
Bisoxyl (*B.D.H.*)—Bismuth oxychloride injection.
Bistovol (*M.B.*)—Bismuth acetarsol.
Borocaine (*B.D.H.*)—Procaine borate.
Butesin (*Ab.*)—Butyl *p*-amino benzoate.
Butolan (*Ba.*)—Diphenan.
Butyn (*Ab.*)—Complex organic local anæsthetic.
B.V.U. (*Ge.*)—Bromoisovalerylurea (an open-chain ureide).

Cafaspin (*Ba.*)—Aspirin and caffeine.
Cafinal (*Ba.*) — Phenobarbitone and caffeine.
Calcibronot (*Sa.*) — Calcium bromolactobionate.
Calcio-coramine (*Li.*)—Double salt of calcium sulphocyanate and niketahmide.
Calciostab (*Bo.*) — Calcium thiosulphate injection.
Calcium Diuretin (*Kn.*)—Theobromine calcium salicylate.
Calcium Sandoz (*Sa.*) — Calcium gluconate.
Calcydic (*A.H.*) — Dicalcium phosphate and vitamin D.
Caloplast (*A.H.*)—Cataplasma kaolini.
Calsiod (*M.J.*)—Calcium ortho-iodoxybenzoate.
Calsimil (*B.H.D.*)—Calcium sodium lactate and vitamin D.
Calsolact (*A.H.*) — Calcium sodium lactate.
Calsoma (*Ab.*)—Tribasic phosphates of calcium and magnesium.
Calsprate (*Ge.*)—Calcium aspirin.
Calsydrol (*Ge.*)—Protein hydrolysate.
Camdelate (*Ab.*)—Calcium mandelate.
Campolon (*Ba.*)—Injectable liver preparation.
Cantan (*Ba.*)—Ascorbic acid.
Caprokol (*B.D.H.*)—Hexylresorcinol.
Carbokaylene (*Ka.*)—Colloidal kaolin and activated charcoal.
Carboserin (*Ba.*)—Medicated charcoal.
Carbrital (*P.D.*)—Carbromal and pentobarbitone.
Cardatone (*Ev.*)—Sodium camphosulphonate.
Cardiazole (*Kn.*)—Leptazol.
Cardone (*P.B.*)—Muscle extract.
Carena (*C.L.*) — Theophylline with ethylenediamine.
Cardophyllin (*Wh.*)—Theophylline with ethylenediamine.
Cargento (*S.D.*)—Mild silver proteinate.
Cascaromat (*Ev.*) — Cascara preparation.
Cebione (*Me.*)—Ascorbic acid.
Cedilanid (*Sa.*)—Lanatoside.
Celin (*Gl.*)—Ascorbic acid.
Cerocol (*Co.*)—Cerium oxalate.
Cetavlon (*I.C.*) — Cetyltrimethyl ammonium bromide.

Cevite (*Op.*)—Cevitamic acid.
Charkaolin (*A.H.*)—Colloidal kaolin and charcoal granules.
Chinosol (*Zi.*) — Potassium hydroxyquinoline sulphate.
Chlorbismol (*M.B.*) — Bismuth oxychloride.
Chlorazene (*Ab.*)—Chloramine.
Chloretone (*P.D.*)—Chlorbutol.
Chlorostab (*Bo.*)—Bismuth oxychloride injection.
Cholesal (*Op.*)—Magnesium sulphate and peptone.
Choryl (*P.P.*)—Carbachol.
Chrimsol (*A.H.*)—Liquid paraffin.
Cibalgin (*Ci.*)—Amidopyrine and allobarbitone.
Cibazon (*Ci.*)—Sulphathiazole.
Cignolin (*Ba.*)—Dithranol.
Citralka (*P.D.*)—Disodium hydrogen citrate preparation.
Clinestrol (*Gl.*)—Stilbœstrol.
Coagulen (*Ci.*)—Hæmoplastin.
Codalgin (*Ba.*)—Aspirin, phenacetin, and codeine.
Codrenine (*P.D.*) — Cocaine and adrenaline for local anæsthesia.
Cofron (*Ab.*)—Liver concentrate with copper and iron.
Cogene (*Ge.*)—Compound codeine tablet.
Colliron (*Ev.*) — Colloidal iron hydroxide.
Collistan (*H.P.*) — Succinyl sulphathiozole.
Collosol (*Cr.*)—Colloidal preparations.
Collozin (*Ev.*) — Colloidal zinc hydroxide.
Collumina (*Ev.*)—Colloidal aluminium hydroxide.
Colonol (*Ka.*)—Liquid paraffin.
Colsulanyde (*Cr.*)—Sulphanilamide.
Coramine (*Ci.*)—Nikethamide.
Cortenil (*Ba.*)—Desoxycorticosterone.
Cortigen (*Ri.*)—Desoxycorticosterone.
Cortin (*Or.*) — Suprarenal cortical extract.
Cortiron (*B.S.*)—Desoxycorticosterone.
Cosylan (*P.D.*)—Compound syrup of cocillana.
Cresibal (*Ev.*)—Bismuth hydroxide and salol cream.
Cresival (*Ba.*)—Calcium cresol sulphonate.
Crisalbine (*M.B.*)—Sodium aurithiosulphate.
Cristodigin (*Li.*) — Crystalline digitoxine.
Crysto-vibex (*P.D.*)—Aneurin hydrochloride.
Cupriferrum (*S.M.*)—Iron and ammonium citrate with copper.
Cyclonal (*M.B.*)—Hexobarbitone.
Cycliton (*R.*)—Carboxylic compound with nikethamide action.
Cystazol (*A.H.*)—Hezamine sodium benzoate.
Cystopurin (*Ge.*)—Hexamine sodium acetate.

Dagenan (*M.B.*)—Sulphapyridine.
Decholin (*Ev.*) — Sodium dehydrocholate.
Decicain (*Ba.*)—Amethocaine.
Dehydrocholin (*B.D.H.*) — Dehydrocholic acid.
Delectol (*D.F.*)—Liquid paraffin.
Dekadexolin (*Gl.*)—Concentrated vitamin A and D.
Dermacrine (*Ba.*) — A flavine antiseptic.
Dermatol (*Ba.*)—Bismuth subgallate.
Derobin (*Ge.*)—Dithranol.
Desibyl (*P.D.*)—Desiccated whole bile.
Dettol (*Re.*)—Roxenol.
Dettolin (*Re.*)—Dimethylchlorophenylhydrate.
Devegan (*Ba.*) — Acetarsol vaginal tablets.
Dexedrine (*M.J.*) — Dextroamphetamine sulphate.
D.H.E. 45 (*Sa.*)—Dihydroergotamine.
Dial (*Ci.*)—Diallylbarbituric acid.
Dialacetin (*Ci.*)—Diallylbarbituric acid and allylparacetaminophenol.
Dibexin (*P.D.*)—Vitamin B-complex.
Dicodid (*R.*)—Dihydrocodeinone.
Didial (*Ci.*)—Ethylmorphine and Dial.
Digalen (*R.*)—Digitalis glycosides.
Digifoline (*Ci.*)—Digitalis glycosides.
Digifortis (*P.D.*)—Digitalis glycosides.
Digiglusin (*Li.*)—Digitalis glycosides.
Digilanid (*Sa.*)—Digitalis lanata glycosides.
Digipuratum (*Kn.*)—Digitalis glycosides.
Diginutin (*B.W.*)—Digitalis glycosides.
Digitalone (*P.D.*)—Digitalis glycosides.
Digitol (*S.D.*)—Digitalis glycosides.
Digiveron (*Co.*)—Digitalis glycosides (mostly gitalin).
Dihaloquin (*S.M.*)—Chiniofon compound.
Dilaudid (*Kn.*) — Dihydromorphinone hydrochloride.
Dimenformon (*Or.*) — Œstradiol benzoate.
Dionin (*S.M.*)—Ethylmorphine hydrochloride.
Dipankrin (*Ri.*)—Pancreatin.
Dismenol (*Ro.*)—Phenazone with *p*-sulphaminobenzoic acid.
Disprin (*Re.*)—Stabilised calcium acetyl salicylate.
Diuretin (*Kn.*) — Theobromine and sodium salicylate.

Diourophylline (*Be.*) — Aminophylline and squill diuretic.
Dolantol (*Ba.*) — Pethidine hydrochloride.
D.O.C.A. (*Or.*)—Desoxycorticosterone acetate.
Doryl (*Me.*)—Carbachol.
Duracaine (*M.B.*)—Procaine benzoate.
Dysco (*Ab.*)—Ephedrine and phenacetin.

Elbon (*Ci.*) — Cinnamolyl - *p* - oxyphenylurea.
Elityran (*Ba.*)—A thyroid extract.
Embinal (*M.B.*)—Soluble barbitone.
Empirin (*B.W.*)—Acetylsalicyclic acid.
Endrine (*Wy.*)—Ephedrine, menthol, etc., in oil.
Enterovioform (*Ci.*)—Complex quinoline and saponin preparation (intestinal antiseptic).
Epanutin (*P.D.*)—Phenytoin.
Ephetonegen (*Ri.*) — Ephedrine and adrenaline preparation.
Ephretuss (*Ev.*) — Syrup containing ephedrine, etc.
Ephresol (*Ev.*)—Ephedrine and adrena line preparation.
Ephregel (*Ev.*)—Ephedrine nasal jelly.
Ephynal (*R.*)—α-tocopherol acetate.
Epinalin (*B.W.*)—Ephedrine and adrenaline preparation.
Eptoin (*Bo.*)—Soluble phenytoin.
Erbolin (*Gl.*)—Total ergot alkaloids.
Ergamine (*B.W.*)—Histamine.
Ergothane (*Ev.*)—Ergotoxine ethaneosulphonate.
Ergotrate (*E.L.*)—An ergometrine salt.
Ernutin (*B.W.*)—Ergotoxine preparation.
Erugon-S (*Ba.*) — Testosterone propionate.
Erythroid (*Oxo*)—Desiccated stomach.
Eschatin (*P.D.*) — Suprarenal cortex extract.
Essogen (*Tr.*)—Vitamin A concentrate.
E.S.T.P. (*Ma.*) — Ether-soluble tar paste.
Etamon (*P.D.*)—Tetraethyl ammonium chloride.
Etelate (*P.D.*)—Ethanolamine oleate.
Ethamolin (*Gl.*)—Ethanolamine oleate.
Etrium (*M.B.*)—Tetræthyl ammonium bromide.
Eubion (*Ev.*)—Vitamin A.
Eucortone (*A.H.*)—Suprarenal cortical extract.
Eugastrol (*A.H.*)—Desiccated stomach.
Eulykol (*B.W.*)—Ethyl esters of hydnocarpus oil.
Eumydrin (*Ba.*) — Methylatropine nitrate.
Euparatone (*P.D.*) — Parathyroid extract.
Euphyllin (*Wh.*)—Theophylline with ethylenediamine.
Evansol (*Ev.*)—Lysol.
Evatmine (*Br.*)—Adrenaline and pituitary compound.
Evidorm (*Ba.*)—Evipan and cyclobarbitone.
Evipan (*Ba.*)—Hexobarbitone-soluble.
Examen (*Gl.*)—Injectable liver extract.
Ex-Lax (*Ex.*)—Phenolphthalein preparation.
Extomak (*Be.*)—Desiccated stomach.

Felamine (*Sa.*) — Hexamine glycocholate.
Femergin (*Sa.*)—Ergotamine tartrate.
Ferascoli (*A.H.*)—Organic iron with nuclein.
Ferrivenin (*Be.*) — Saccharated iron oxide for intravenous injection.
Ferro-redoxon (*R.*)—Ferrous iron with vitamin C.
Ferosan (*Bo.*) — Citrated ferrous chloride.
Ferratin (*Co.*) — Sodium ferroalbuminate.
Ferroarsine (*P.D.*)—Iron and arsenic peptone compound.
Ferro-constans (*Ri.*)—Ferrous chloride.
Ferrodic (*A.H.*)—Ferrous phosphate in chocolated granules.
Ferrofax (*Cr.*)—Ferrous iron with vitamin B.
Ferroglanoid (*Arm.*)—Liver extract and ferri ammon. citrate.
Fersolate (*Gl.*)—Compound ferrous sulphate tablets.
Fertilol (*Vi.*)—Wheat-germ oil.
Festan (*Be.*)—Pancreatin.
Flavazole (*Bo.*)—Proflavine and sulphathiazole.
Flavogel (*Gl.*)—A flavine antiseptic jelly.
Folvite (*Le.*)—Folic acid.
Folvron (*Le.*)—Folic acid and ferrous sulphate.
Fotomeals (*Ev.*)—Barium sulphate meals.
Fouadin (*Ba.*)—Stibophen.
Franol (*Ba.*)—Phenobarbitone, aloin, ephedrine.

Gardan (*Ba.*)—Novalgin an amidopyrin.
Gardenal (*M.B.*)—Phenobarbitone.
Gaster Siccita (*B.D.H.*)—Desiccated stomach.
Gastomag (*Bo.*)—Magnesium trisilicate.
Gastrexo (*Ev.*)—Desiccated stomach.
Genasprin (*Ge.*)—Acetylsalicylic acid.

Gelusil (*W.W.*)—Colloidal aluminium hydroxide and magnesium trisilicate.
Genaformamint (*Ge.*) — Formamint tablets.
Genocaine (*Ge.*) — Procaine hydrochloride.
Genophyllin (*Ge.*)—Aminophylline.
Germanin (*Ba.*)—Suramin.
Germinol (*P.B.*)—Wheat-germ oil.
Germosan (*Ge.*)—Chloroxylenol antiseptic.
Gestone-oral (*P.B.*)—Ethisterone.
Gestyl (*Or.*)—Gonadotrophic hormone from mares' serum.
Gevilon (*Ba.*)—Crystal violet.
Glandiposan (*Ri.*) — Thyroid and pituitary extract.
Glandubolin (*Ri.*)—Œstrone.
Glanduitrin (*Ri.*)—Pituitary extract.
Glucodin (*Gl.*)—Glucose and vitamin D.
Glucophyllin (*Ab.*) — Theophylline and methylglucamine.
Glandothrophon (*P.B.*) — Chorionic gonadotrophin.
Gonacrine (*M.B.*)—Euflavine.
Gonadyl (*Rou*)—Serum gonadotrophin.
Gonan (*B.D.H.*)—Chorionic gonadotrophin.
Gynœstryl (*Rou.*)—Œstradiol.
Gynosone (*I.C.*) — Triphenylchlorethylene.

Hæmagulen (*Li.*)—Hæmostatic preparation.
Hæmex (*P.B.*)—Liver preparation.
Hæmoplastin (*P.D.*) — Hæmostatic serum.
Halibol (*A.H.*)—Halibut-liver oil.
Haliborange (*A.H.*)—Halibol with concentrated orange juice.
Halidexol (*Cr.*) — Halibut-liver oil emulsion.
Halimalt (*Cr.*)—Halibut-liver oil and malt.
Haliver Oil (*Ab.*)—Halibut-liver oil.
Haliverol (*P.D.*)—Halibut-liver oil with added vitamin D.
Halivita (*Ri.*)—Halibut-liver oil preparation.
Halivite (*Sc.*)—Halibut-liver oil preparation.
Halycalcyne (*Cr.*) — Halibut-liver oil with calcium phosphate.
Hebarol (*P.D.*)—Sodium hexyl ethyl barbiturate.
Helmitol (*Ba.*)—Formamol.
Hemochromin (*Bro.*)—Exsiccated ferrous sulphate.
Hepamino (*Ev.*)—Oral proteolysed liver.
Hepamult (*No.*)—Oral liver preparation.
Heparglandol (*Br.*) — Injectable liver extract with vitamin B.
Heparmone (*Li.*)—Liver preparation.
Hepastab (*Bo.*)—Injectable liver preparation.
Hepatexoral (*Ev.*)—Oral liver extract.
Hepatex T (*Ev.*)—Injectable crude liver extract.
Hepicoleum (*Li.*)—Vitamin A and D.
Hepolon (*A.H.*) — Injectable liver extract.
Hexanastab (*Bo.*)—Soluble hexobarbitone.
Hexyltan (*S.D.*)—Hexylresorcinol and tannic acid.
Hoggex (*P.B.*) — Desiccated hog's stomach.
Holocain (*Ba.*)—Phenacaine hydrochloride.
Hombreol (*Or.*)—Androsterone.
Hydantol (*B.W.*)—Phenytoin soluble.
Hydronal (*Ba.*)—Aluminium hydroxide.
Hypophysin (*Ba.*)—Liquid extract of pituitary posterior lobe.

Iberin (*Ab.*)—Iron and ammonium citrate, vitamin B_1, liver.
Ichthyol—Ichthammol.
Idozan (*Co.*)—Colloidal iron.
Iliren (*Ba.*) — Suprarenal cortical extract.
Imadyl (*R.*)—Histamine preparation.
Infundin (*B.W.*)—Pituitary posterior lobe extract.
Infundrenalin (*Ev.*)—Pituitary posterior lobe extract, plus adrenaline.
Intraval Sodium (*M.B.*)—Soluble thiopentone.
Iodatol (*B.D.H.*)—Iodised oil.
Iodex (*M.J.*)—Non-staining iodine ointment, B.P.C.
Iodicin (*B.W.*) — Calcium iodo-ricinoleate.
Iodinol (*Ma.*)—Iodised oil.
Iodolysin (*A.H.*)—Thiosinamine and iodine compound.
Iodoprotein (*Ma.*)—Iodine compound.
Iodoray (*Ma.*)—Sodium ortho-iodohippurate (for pyelography).
Iodostarin (*R.*)—Iodine compound.
Iolase (*A.F.*)—Iodine albumose compound.
Ioxantin (*Op.*)—Organic iodine compound.
Ipecopan (*Sa.*)—Active principles of opium and ipecacuanha.
Isoflav (*Bo.*)—Isotonic proflavine solution.
Isogel (*A.H.*)—Bulk-forming vegetable laxative.
Istin (*Ba.*)—Anthraquinine purgative.
Ivax (*Bo.*)—Liquid extract of apples.

Jectemia (*S.D.*) — Injectable liver extract.
Jecomalt (*Wan.*)—Dried malt extract and cod liver oil.

Kalmopyrin (*Ri.*)—Calcium acetylsalicylate.
Kalzana (*T.P.*) — Calcium sodium lactate.
Kapilon (*Gl.*)—Menaphthone.
Kappaxan (*Ba.*)—Menaphthone.
Kaylene (*Ka.*)—Colloidal kaolin.
Kaylene-ol (*Ka.*)—Kaolin and liquid paraffin preparation.
Kemithal (*I.C.*)—Sodium cyclohexenylalkyl-barbiturate.
Kayvysin (*P.D.*)—Vitamin K.
Keturex (*Ev.*)—Ammonium mandelate.
Kharophen (*B.W.*)—Acetorsol.
Kharsulphan (*B.W.*)—Sulpharsphenamine.
Klotogen (*Ab.*)—Vitamin K.
Koplon (*Or.*)—Œstrone and glucose preparation for vaginal medication.
Koptalgos (*D.F.*) — Preparation of opium.

Lactalumina (*Cr.*)—Colloidal aluminium hydroxide.
Lacta-calamine (*Cr.*) — Colloidal calamine.
Larostidine (*R.*)—1-histamine hydrochloride.
Laverin (*A.H.*)—Preparation of bacteria producing lactic acid.
Laxoin (*Op.*)—Phenolphthalein.
Lertigon (*P.D.*)—Histamine azoprotein.
Leucarsone (*M.B.*)—Carbasone.
Lipoiodine (*Ci.*)—Organic iodine compound.
Lipiodol (*Bg.*)—Iodised oil.
Lipobismol (*P.D.*)—Bismuth octyl oxyacetate.
Lipolutin (*P.D.*)—Progesterone.
Liquemin (*R.*)—Heparin preparation.
Liquoid (*R.*)—Anticoagulant substance.
Livadex (*B.D.H.*)—Liver extract.
Livogen (*B.D.H.*)—Liver extract, yeast, vitamin B.
Lixen (*A.H.*)—Liquid senna preparation.
Lacarnol (*Ba.*)—A tissue extract used as a vaso-dilator.
Locosthetic (*P.D.*)—Cocaine and adrenaline injection.
Loricide (*I.C.*)—Laurylthiocyanate preparation.
Luminal (*Ba.*)—Phenobarbitone.
Lunargen (*Li.*)—Mild silver proteinate.
Luteoantin (*Ri.*)—Serum gonadotrophin.
Luteostab (*Bo.*)—Progesterone.
Lutocyclin (*Ci.*)—Progesterone.
Lutren (*Ba.*)—Progesterone.
Lysantol (*A.H.*)—Roxenol.

M. & B. 693 (*M.B.*)—Sulphapyridine.
M. & B. 760 (*M.B.*)—Sulphathiazole.
Magsorbent (*Ka.*)—Magnesium trisilicate.
Mandecal (*B.D.H.*)—Calcium mandelate.
Mandelix (*B.D.H.*)—Ammonium mandelate elixir.
Mapharside (*P.D.*)—A spirochœticidal arsenical.
Marprontil (*Ba.*)—Sulphabenzamine.
Medinal (*Sch.*)—Soluble barbitone.
Menformon (*Or.*)—Œstrone preparation.
Menopax (*C.P.*)—Stilbœstrol with sedatives.
Mercurocol (*Ev.*)—Mercurochrome.
Mercurome (*Ma.*)—Mercurochrome.
Merfenil (*M.B.*) — Phenylmercuric nitrate preparation.
Mersogel (*Gl.*)—Phenylmercuric acetate preparation.
Merthiolate (*Li.*)—Organic mercurial antiseptic.
Metaphen (*Ab.*)—Organic mercurial antiseptic.
Metarsenobillon (*M.B.*) — Sulpharsphenamine.
Metasilia (*Ab.*)—A liquid paraffin emulsion.
Meteph (*M.M.P.*)—Methyl ephedrine.
Methedrine (*B.W.*)—Desoxyephedrine.
Methergin (*Sa.*)—Methyl ergometrine tartrate.
Metramine (*Ab.*)—Hexamine.
Metycaine (*Li.*) — Piperidine alkyl benzoate (local anæsthetic).
Milk of Magnesia (*Ph.*)—A magnesium hydroxide suspension.
Migrainine (*Ba.*)—Phenazone and caffeine citrate.
Mil-Par (*Ph.*)—Magnesia and liquid paraffin.
Molevac (*P.D.*)—Extract of malt with liquid paraffin and cascara.
Monolate (*Ab.*) — Monœthanolamine oleate injection.
Moramine (*A.H.*)—Ethanolamine oleate injection.
Moryl (*S.M.*)—Carbachol.
Mycil (*B.D.H.*) — Chloro-phenyl-glycerol ether.
Myocrisin (*M.B.*)—Gold sodium thiomalate.
Myodil (*Gl.*)—Iodophenyl compound for spinal myelography.
Myosalvarsan (*Ba.*)—Sulpharsphenamine.

Nadola (*P.D.*)—Vitamin A and D.
Naferon (*P.D.*)—Iron and sodium citrate.
Nativelle's Digitalein (*Nat.*) — Digitoxine.
Nargol (*P.D.*)—Silver nucleide.
Navigan (*R.*)—Sedative tablets for travel sickness.
Nembutal (*Ab.*) — Soluble pentobarbitone.
Neo-Epinine (*B.W.*)—Isopropyl noradrenaline sulphate.
Neofemergin (*Ab.*) — Ergometrine and ergotamine tartrate.
Neoferrum (*Cr.*)—Colloidal ferric hydroxide.
Neohalarsine (*M.B.*) — Oxyphenarsine tartrate.
Neohepatex (*Ev.*)—Concentrated injectable liver extract.
Nembudeine (*Ab.*)—Nembutal, phenacetin and codeine.
Neo-œstrandl (*Cr.*)—Stilbœstrol.
Neo-Hombreol (*Or.*)—Testosterone propionate.
Neo-Hydriol (*M.B.*)—Iodised oil.
Neoket (*Bo.*)—Mandelic acid preparation.
Neokharsivan (*B.W.*)—Neoarsphenamine.
Neomonsol (*M.L.*)—Roxinol.
Neoprotosil (*P.D.*)—Colloidal silver iodide.
Neovaricane (*M.B.*) — Monœthanolamine oleate injection.
Nepenthe (*Fe.*) — Liquid preparation of opium, four-fifths the strength of official tincture.
Neptal (*M.B.*)—Mercurial diuretic.
Niagrin (*Ba.*)—Nicotinamide.
Nicamide (*B.W.*)—Nikethamide.
Nicorbin (*Gl.*)—Nicotinic acid, aneurin, and ascorbic acid.
Nikethanol (*Ba.*)—Nikethamide.
Nipectin (*Li.*)—Preparation of pectin.
Normacol (*No.*)—Bulk-forming vegetable laxative.
Novacrysin (*Nap.*)—Sodium aurithiosulphate.
Novalgin (*Ba.*)—An amidopyrin derivative.
Novarsan (*A.H.*)—Neoarsphenamine.
Novasorb (*Ev.*)—Magnesium trisilicate.
Novasurol (*Ba.*)—Merbaphen.
Novocain (*Ba.*) — Procaine hydrochloride.
Novocaine (*Sac.*) — Procaine hydrochloride.
Novostab (*Bo.*)—Neoarsphenamine.
Novutox (*P.M.*)—Self sterilising solution of procaine.
Nujol (*Ste.*)—Liquid paraffin.
Nupercaine (*Ci.*)—A local anæsthetic.
Œstroform (*B.D.H.*)—Œstrogen preparation.
Oladol (*Ab.*)—Halibut-liver oil and vitamin D.
Olgar (*P.D.*)—Emulsion of liquid paraffin and agar.
Omnopon (*R.*)—Papaveretum, B.P.C.
Opacin (*M.B.*)—Iodophthalein.
Opacol (*M.B.*)—Preparation of iodophthalein for oral use.
Opoidine (*Mac.*)—Papaveretum, B.P.C.
Optalidon (*Sa.*)—Sandoptal, amidopyrin, and caffeine.
Optochin (*Ho.*)—A quinine derivative.
Orarsan (*Bo.*)—Acetarsol.
Oraviron (*B.S.*)—Methyltestosterone.
Oridin (*Li.*)—Fatty acid compound and iodine.
Orthoform (*Ba.*)—Orthocaine.
Osmokaolin (*A.H.*)—Colloidal kaolin.
Ostelin (*Gl.*)—Calciferol.
Ostocalcium (*Gl.*)—Calcium and calciferol tablets.
Osyl (*Ly.*)—A chloroxylenol antiseptic.
Otalgan (*Nap.*)—Phenazone in glycerin.
Ovendosyn (*M.J.*)—Stilbœstrol and calcium phosphate.
Ovocyclin (*Ci.*)—Œstradiol.
Ovoferrin (*Fa.*)—Colloidal iron preparation.
Oxylan (*B.W.*)—Diphenan.

Pabestrol (*P.B.*)—Stilbœstrol.
P.A.B.S. (*He.*)—Sulphanilamide.
Padutin (*Ba.*)—Arteriolar dilator extracted from pancreas.
Paludrin (*I.C.*)—Biguanide antimalarial compound.
Panflavine (*Ba.*)—Euflavine.
Panlittol (*Arm.*)—Pancreatin.
Panteric Tablets (*P.D.*)—Pancreatin.
Panthesine (*Sa.*)—Ester of para-aminobenzoic acid (local anæsthetic).
Paracascar (*Ev.*)—Liquid paraffin and cascara.
Paragar (*Ev.*)—Liquid paraffin emulsion.
Parakaolin (*D.F.*)—Kaolin and liquid paraffin emulsion.
Paramisal (*H.P.*)—Para-amino salicylic acid.
Paraphen (*Ev.*)—Liquid paraffin and phenolphthalein.
Parathormone (*Li.*) — Parathyroid extract.
Paredrine (*M.J.*)—A vasoconstrictor.
Parenamps (*P.B.*)—Injectable liver preparation.
Parmanil (*Ba.*)—Methyl glucamide of aurothioglycollic acid.
Paromin (*P.B.*)—Thyroid preparation.

Paroidin (*P.D.*)—Parathyroid extract.
Paroleine (*P.D.*)—Light liquid paraffin.
Parsetic (*P.D.*)—Procaine and adrenaline injection.
Pellidol (*Ba.*)—Scarlet red.
Pelonin (*Gl.*)—Nicotinic acid.
Pentide (*A.H.*)—Sodium pentose nucleo.
Pentide (*A.H.*) — Sodium pentose nucleotide.
Pentnucleotide (*M.J.*)—Sodium pentose nucleotide.
Pentothal (*Ab.*)—Thiopentone soluble.
Pepsac (*Bo.*)—Desiccated stomach.
Perabrodil (*Ba.*)—Diodone.
Perandren (*Ci.*)—Testosterone propionate.
Percalcin (*Ev.*)—Injectable organic calcium compound.
Percorten (*Ci.*)—Desoxycorticosterone acetate.
Perhydrol (*S.M.*)—Hydrogen peroxide (100 vol.).
Perichthol (*B.D.H.*)—Ichthammol.
Permidin (*Gl.*)—Hesperidin.
Pernæmon Forte (*Or.*)—Injectable liver preparation.
Pernivite Tablets (*B.D.H.*)—Vitamin K with nicotinic acid.
Petromag (*Ev.*)—Liquid paraffin and magnesia.
Petronol (*Op.*)—Liquid paraffin.
Phanodorm (*Ba.*)—Cyclobarbitone.
Phedros (*S.D.*)—Ephedrine syrup.
Phemeride (*P.D.*)—Complex antiseptic compound.
Phenoquin (*Sou.*)—Cinchophen.
Phenoxetol (*Ni.*) — Phenoxy - ethyl alcohol.
Pholetone (*Bo.*)—Pholedrine.
Phosphomandelate (*Cr.*)—Mandelic acid and ammonium phosphate.
Phrenazol (*Bo.*)—Leptazol.
Physeptone (*B.W.*)—Complex analgesic.
Physolactin (*Gl.*)—Lactogenic preparation of anterior pituitary.
Physostab (*Bo.*)—Urine gonadotrophin.
Phytoferol (*B.D.H.*)—Wheat-germ concentrate.
Pitrenalin (*P.D.*)—Pituitary extract and adrenaline.
Pitibulin (*A.H.*)—Posterior lobe of pituitary extract.
Pitocin (*P.D.*)—Oxytocic principle of posterior pituitary.
Piton (*Or.*)—Posterior pituitary extract.
Pitoxylin (*Oxo*) — Posterior pituitary extract.
Pitressin (*P.D.*)—Pressor principle of posterior pituitary.
Pituitrin (*P.D.*)—Posterior pituitary lobe extract.
Planacrine (*M.B.*)—Euflavine lozenges.
Phanadalin (*M.B.*)—Carbromal.
Planavit B. (*M.B.*)—Aneurin hydrochloride.
Planocaine (*M.B.*)—Procaine hydrochloride.
Planochrome (*M.B.*)—Mercurochrome.
Planoform (*M.B.*)—Butiform.
Plasmoquin (*Ba.*)—Pamaquin.
Plexan (*Gl.*)—Injectable crude liver extract.
Polyansyn (*Arm.*)—Anterior pituitary hormones.
Pontocaine (*Wyn.*)—Butethanol.
Præquine (*M.B.*)—Pamaquin.
Pragmoline (*M.B.*) — Acetylcholine bromide.
Pregnyl (*Or.*)—Gonadotrophic hormone from pregnancy urine.
Preloban (*Ba.*) — Whole anterior pituitary extract.
Prepalin (*Gl.*)—Vitamin K.
Priovit (*Ba.*)—Vitamins B_1, B_2, C and P.
Privine (*Ci.*)—Imidazoline vasoconstrictor compound.
Proctocaine (*A.H.*) — Oily injection containing procaine.
Prœthron (*Arm.*)—Injectable concentrated liver extract.
Profecundum (*Ri.*)—Wheat-germ oil.
Progestoral (*Or.*)—Ethisterone.
Progynon (*B.S.*)—Œstrogen preparation.
Prokayvit (*B.D.H.*) — Menapthone.
Prolan (*Ba.*) — Gonadotrophic hormone.
Prolutone (*B.S.*) — Progesterone.
Promanide (*P.D.*)—Promine compound.
Prominal (*Ba.*)—Phemitone.
Prontosil Album (*Ba.*)—Sulphanilamide.
Prontosil Rubrum (*Ba.*)—A sulphanilamide dye complex.
Pronutron (*H.P.*)—Casein hydrolysate.
Propadrin (*S.D.*) — Propanolamine hydrochloride with ephedrine-like action.
Proscabin (*Ba.*) — Benzyl benzoate application.
Proseptasine (*M.B.*) — Benzyl sulphanilamide.
Prothricin (*G.D.*) — Thyrothricin and propadin.
Prostigmine (*R.*) — Synthetic physostigmine analogue.
Protargol (*Ba.*)—Silver proteinate.
Protosil (*P.D.*)—Mild silver proteinate.
Proviron (*Sch.*) — Androsterone benzoate.
Psylla (*Co.*)—Bulk-forming vegetable laxative.
Purgen (*Ki.*)—Phenolphthalein tablets.

Pyelectan (*Gl.*)—Iodoxyl.
Pyelosil (*Gl.*)—Diodone.
Pyelumbrin (*Bo.*)—Iodoxyl.
Pyramidon (*Ba.*)—Amidopyrin.
Pyridium (*M.J.*)—Phenylazo-diamino pyridine.

Quinacrine Soluble (*M.B.*)—Mepacrine methanesulphonate.
Quinio-Stovarsol (*M.B.*) — Quinine acetarsol.
Quinolor (*S.M.*)—Ointment containing chlorhydroxyquinoline.
Quino-Plasmoquine (*Ba.*)—Quinine sulphate and pamaquin.
Quinostab (*Bo.*) — Quinine iodobismuthate.
Quinoxyl (*Ba.*)—Chinioform.

Rabellon (*S.D.*)—Hyoscyamine, atropine, and scopolamine.
Radiomalt (*B.H.D.*)—Malt extract with vitamins A, B, D.
Radiostol (*B.D.H.*)—Vitamin D concentrate.
Radiostoleum (*B.D.H.*)—Vitamin A and D concentrate.
Redoxon (*R.*)—Ascorbic acid.
Renaglandin (*Op.*)—Adrenaline.
Riodine (*M.J.*)—Iodised castor oil.
Rubiazol (*Rou.*)—A sulphanilamide dye complex.
Rubyl (*M.B.*)—Bismuth and quinine iodide in oily suspension.
Ruscoin (*Ev.*) — Resorcin compound ointment.
Rutin (*A.H.*) — Flavanol glycoside (vitamin P).
Rutonal (*M.B.*)—A barbiturate.
Rusven (*Bo.*)—Russell's viper venom.

Sal-ethyl-carbonate (*P.D.*) — Salicylic ethyl ester carbonate.
Sajodin (*Ba.*)—Iodine compound.
Salophen (*Ba.*) — Acetyl para-amido salol.
Salyrgan (*Ba.*)—Mersalyl injection.
Sandoptal (*Sa.*) — A barbiturate (hypnotic).
Saridone (*R.*)—Analgesic of phenacetin, phenazone, caffeine type.
S.B.T. (*He.*)—Sodium bismuthyl tartrate.
Scabenzol (*Bo.*)—Benzyl benzoate.
Scillaren (*Sa.*)—Squill glycoside.
Scuroform (*M.B.*)—Butoform.
Seconal (*Li.*)—A barbiturate.
Sedobrol (*R.*) — Sodium bromide bouillon tablet.
Sedormid (*R.*) — Allylisopropylacetyl urea.
Seroden (*A.H.*)—Iodine protein compound.
Serogan (*B.D.H.*)—Gonadotrophic hormone from mares' serum.
Sevicaine (*Gl.*)—Procaine.
Shadoform (*B.D.H.*)—Barium meal.
Sionon (*Ba.*)—Sorbitol.
Sketofax (*B.W.*)—Dimethyl phthalate preparation.
Soamin (*B.W.*) — Sodium aminoarsenate.
Solantoin (*Gl.*) — Sodium diphenylhydantoinate.
Solganol B (*B.S.*)—Aurothioglucose.
Solurol (*A.H.*)—Thyminic acid.
Soluseptasine (*M.B.*) — An injectable sulphonamide.
Soluthiazole (*M.B.*)—Neutral soluble sulphathiazole.
Somnifaine (*R.*) — A complex barbiturate.
Somnigen (*Arm.*)—Opium wine.
Somnos (*S.D.*)—Elixir of chloral glycerolate.
Sonalgin (*M.B.*) — Butophen with codeine.
Soneryl (*M.B.*)—Butyl ethyl barbituric acid.
Spasmolyth (*W.P.*) — Phenapyrine caffeine.
Spirocid (*Ba.*)—Acetarsol.
Stabilarsan (*Bo.*)—Arsphenamine diglucoside.
Stabismol (*Bo.*)—Injection of oil soluble bismuth.
Staniform (*Wh.*)—Methyl stannic iodide.
Stannoxyl (*A.F.*) — A preparation of tin.
Sterandryl (*Rou.*)—Testosterone propionate.
Stipolac (*B.W.*)—Iodophenolphthalein.
Stilbagen (*He.*)—Dihydroxydiethyl stilbene, phenobarbitone compound.
Stovaine (*M.B.*) — Amylocaine hydrochloride.
Stovarsol (*M.B.*)—Acetarsol.
Streptocide (*Ev.*)—Sulphanilamide.
Strophosid (*Sa.*)—A strophantus glycoside.
Stypven (*B.W.*) — Russell's viper venom.
Sudermo (*B.W.*)—Mesulphen.
Sulfamerazine (*S.D.*) — Monomethyl sulphapyrimidine.
Sulfarsenol (*M.P.*) — Sulpharsphenamine.
Sulfasuxidine (*S.D.*) — Succinyl sulphathiazole.
Sulfathalidine (*S.D.*) — Phthalylsulphathiazole.
Sulphamezathine (*I.C.*) — Dimethyl sulphapyrimidine.

Sulphatriad (*M.B.*)—Sulphathiazole, sulphamerazine, and sulphadiazine compound.
Sulphonamide P. (*B.W.*)—Sulphanilamide.
Sulphostab (*Bo.*)—Sulpharsphenamine.
Sumonal (*Ri.*)—Phenobarbitone.
Suprachol (*Ri.*)—Sodium dehydrocholate.
Supracort (*P.B.*)—Suprarenal cortical extract.
Suprarenalin (*Arm.*)—Adrenaline.
S.V.C. (*M.B.*)—Acetarsol vaginal compound.
Synapoidin (*P.D.*)—Chorionic gonadotrophin and anterior pituitary extract.
Syncortyl (*Rou.*)—Desoxycorticosterone acetate.
Synkavit (*R.*)—Vitamin K.
Synthevo (*Bo.*)—Hexœstrol.
Syntropan (*R.*)—Synthetic atropine analogue.

Taka-Bexin (*P.D.*)—Diastase, vitamins B and C.
Taka-Diastase (*P.D.*)—Diastase-like substance.
Tannafax (*B.W.*)—Tannic acid jelly.
Taroxide (*Ab.*)—Coal-tar distillate ointment.
Temparin (*H.P.*)—Dicoumarin.
Tenebryl (*Bg.*)—Di-iodo methane sulphonate compound for pyelography.
Testoviron (*Sch.*)—Testosterone propionate.
Tetmosol (*I.C.*)—Tetræthyl thiuram monosulphide.
Tetracap (*B.W.*)—Tetrachlorethylene.
Tetraform (*B.D.H.*)—Carbon tetrachloride.
Thalazole (*M.B.*)—Phthalylsulphathiazole.
Thalistatyl (*H.P.*)—Phthalylsulphathiazole.
Thanomin (*B.W.*)—Monœthanolamine oleate injection.
Theelin (*P.D.*)—Œstrogenic hormone.
Thelestrol (*Bro.*)—Hexœstrol and phenobarbitone.
Theoba (*B.W.*)—Theobromine and phenobarbitone.
Theocin (*Ba.*)—Theophylline.
Theogardenal (*M.B.*)—Theobromine and phenobarbitone tablets.
Theominal (*Ba.*)—Theobromine and phenobarbitone tablets.
Theosal (*Ev.*)—Theobromine sodium salicylate.
Thermotabs (*S.D.*)—Sodium chloride and dextrose tablets.
Thiazamide (*M.B.*)—Sulphathiazole.
Thiobismol (*P.D.*)—Sodium bismuth thioglycollate.
Thiostab (*Bo.*)—Sodium thiosulphate injection.
Thromboplastin (*P.D.*)—Hæmostatic compound.
Thrombin Coagulent (*Maw*)—Hæmostatic compound.
Thyranon (*Or.*)—Thyroid extract.
Thyrin (*Ri.*)—Thyroid for injection.
Thyrocoids (*Co.*)—Thyroid tablets.
Thyroantin (*Ri.*)—Thyrotropic hormone from anterior pituitary.
Thyrogan (*B.D.H.*)—Thyrotropic hormone from anterior pituitary.
Thyroprotein (*P.D.*)—Thyroid extract.
Thyrotropin (*P.B.*)—Thyrotropic hormone from anterior pituitary.
T.I.P. (*Bo.*)—Iodophthalein.
T.I.P.P. (*B.D.H.*)—Iodophthalein.
Tolamine (*B.W.*)—Chloramine.
Tolysin (*Ma.*)—Neocinchophen.
Tonephin (*Ba.*)—Pressor principle from posterior pituitary.
Tophosan (*Ri.*)—Cinchophen.
Trasentin (*Ci.*)—Synthetic antispasmodic compound.
Tridestrin (*P.B.*)—Œstriol tablets.
Trigol (*Ab.*)—Wheat-germ oil.
Trilactine (*Ma.*)—Lactic acid bacteria.
Trilene (*I.C.*)—Trichlorethylene.
Trineemia (*S.M.*)—Iron compound with yeast.
Triodone (*Ab.*)—Trimethyl oxazolidinedione.
Triofax (*B.W.*)—Triple dye jelly.
Trional (*Ba.*)—Methyl sulphonal.
Trypaflavine (*Ba.*)—Euflavine.
Tuamine (*Li.*)—2-Aminoheptane (vasoconstrictor substance).

Uleron (*Ba.*)—A sulphonamide.
Unden (*Ba.*)—Œstrone.
Oriodone (*M.B.*)—Diodone solution.
Uropac (*M.B.*)—Iodoxyl.
Uroselectan B (*Sch.*)—Iodoxyl.
Urotropine (*Sch.*)—Hexamine.
Urumbrin (*Bo.*)—Iodoxyl.

Varicane (*M.B.*)—Sodium morrhuate injection.
Varistab (*Bo.*)—Ethanolamine oleate injection.
Varixol (*Ev.*)—Quinine urethane injection.
Vasoconstrictine (*D.F.*)—Adrenaline.
Veganin (*W.W.*)—Compound codeine tablets.
Ventræmon (*Or.*)—Desiccated hog's stomach.

Ventrax (*P.D.*)—Hog's stomach, ferrous sulphate, vitamin B.
Ventriculin (*P.D.*)—Desiccated hog's stomach.
Veramon (*B.S.*)—Amidopyrine and barbitone.
Vercolate (*Wan.*)—Bile salts, cascara, phenolphthalein.
Veritol (*Kn.*)—Pholedrine.
Veronal (*Ba.*)—Barbitone.
Veropyron (*Ri.*) — Amidopyrin and barbitone.
Vesalvine (*Ma.*)—Hexamine.
Vibelan (*B.D.H.*)—Vitamin B-complex.
Vitmaltol (*Wan.*)—Malt extract, cod liver oil, and vitamin C.
Vince (*W.W.*)—Sodium perborate, etc.
Vinesthene (*M.B.*)—Vinyl ether.
Virormone (*P.B.*)—Testosterone.
Virormone-oral (*P.B.*)—Methyl testosterone.
Viteolin (*Gl.*)—Wheat-germ oil concentrate.

Wintrozole (*Ba.*)—Sulphathiazole.

Yatren (*Ba.*)—Chiniofon.

Zant (*Ev.*)—Parachlormetaxylenol antiseptic.
Zygon (*Sq.*)—Vitamin E.

A CONCISE PHARMACOLOGY AND THERAPEUTICS

ROUTES BY WHICH DRUGS ARE ADMINISTERED

Oral Medication.

When taken by mouth a drug may be intended to have a purely local action on the alimentary tract (*e.g.* liquid paraffin), or to exert its effect by reflex therefrom (*e.g.* ammonium carbonate). If it is desired, however, that the drug should get into the blood-stream, then the factor of diffusibility from the tract must be considered. Obviously no direct systemic benefit can be derived from a substance which, taken by mouth, remains unabsorbed and finally is excreted by the bowel (*e.g.* magnesium sulphate). Another important consideration is the chemical reactivity of the pepsin and hydrochloric acid of the stomach, and of the alkaline juices and digestive ferments of the intestine. On this account some valuable drugs (*e.g.* adrenaline) are completely inactivated when taken by mouth and other ways of introducing them into the system must be found. If the acid gastric secretion, only, is to be avoided, the drug can sometimes be put into soft gelatin capsules, which are then exposed to the action of formaldehyde. This treatment renders the gelatin insoluble in an acid, pepsin solution, but soluble in an alkaline solution of pancreatin. This, and other methods designed to the same end, is termed "enteric coating." Some important drugs produce much nausea or vomiting by their irritant action on the gastric mucosa (*e.g.* emetine hydrochloride) and to administer them orally in adequate dosage is impossible. Enteric coating is sometimes used to get over this difficulty, but not always very successfully, because irritation of the mucosa of the duodenum will just as readily set up a reflex to the vomiting centre as gastric irritation. Finally, it must be remembered that very few substances indeed are absorbed directly from the stomach. Alcohol is partly so absorbed, and this accounts for the rapidity with which it acts, especially when the stomach is nearly empty. Other substances have to reach the small intestine before absorption can take place, so an inevitable delay occurs before the onset of their action. The actual time-lag involved depends a lot on whether the stomach contains much in the way of food when the dose is taken. It is generally true, however, that a small dose of alkali, such as sodium bicarbonate, will expedite the passage of a drug into the intestine by helping the pyloric sphincter to relax.

Sub-lingual Absorption.

Some substances are well absorbed by the sub-lingual epithelial cells, and this, at times, forms a convenient route of administration. Glyceryl trinitrate, which is used for the prevention and treatment of anginal spasm, is rapidly absorbed by the buccal mucosa and it is used incorporated into small chocolate tablets, which melt under the tongue. Another interesting example is the treatment of infantile pyloric stenosis by means of atropine methyl nitrate (*q.v.*). If the infant is permitted to swallow the dose little benefit results because the vomiting and pylorospasm may prevent the drug reaching the intestine, and it is not absorbed from the stomach. A drop or two of solution, or a tiny gelatin disc (lamella) containing the drug, placed under the infant's tongue permits effective medication.

Absorption from the Nasal Mucosa.

A few substances are readily absorbed when snuffed into the nose. A well-known example is, of course, cocaine hydrochloride, which, at one time, was widely self-administered in this way by addicts. This drug rapidly reaches the blood-stream and its characteristic effects become noticeable within a few moments. Gangrene of the nasal mucous membrane eventually follows the prolonged local vasoconstriction to which cocaine gives rise. A snuff containing exsiccated posterior lobe of the pituitary is used in the control of diabetes insipidus.

Inhalation.

When a volatile substance is inhaled it may be absorbed from the naso-pharynx and the lungs. Sometimes a reflex stimulation of the bulbar centres from the naso-pharynx is required. Thus smelling-salts (perfumed ammonium carbonate), strong acetic acid or burning feathers may be placed under the nostrils of a fainting person. Other substances, intended to be absorbed when inhaled, are amyl nitrite for the relief of cardiac pain and trichlorethylene against trigeminal neuralgia, etc. **Aerosols** are vapours or mists of chemical compounds used either for killing organisms or insects in the air (see Insecticides) or for their anti-bacterial effect following inhalation, *e.g.* penicillin, streptomycin, etc. Finally, to this group belong all the volatile anæsthetics.

Rectal Administration.

An enema is a volume of fluid intended for injection into the rectum. Enemata may be administered purely for the purpose of purgation (*e.g.* soap enema), to treat local lesions of the tract as in the use of a dilute solution of silver nitrate in cases of ulcerative colitis, or to introduce some drug intended for absorption from the rectum. Large doses of chloral hydrate, for example, intended to control convulsions, are too nauseous to be tolerated orally, but the drug may be given per rectum dissolved in a little thin mucilage of starch to minimise irritation of the mucous membrane. Normal saline, and basal narcotics, such as bromethol and paraldehyde, are given by the same route and for the same reason. Another point to be considered is that drugs administered rectally are absorbed, to some extent, by the inferior hæmorrhoidal plexus and miss the portal circulation. In consequence they are able to exert a physiological action prior to any detoxication by the liver. Another medium for rectal medication is the suppository. Suppositories are torpedo-shaped, weigh from one to two grammes, and are normally made with a basis of cocoa-butter or glycerinated gelatin. The former is a solid at normal room temperature but melts slightly below body-temperature, glycerinated gelatin readily absorbs water after insertion into the rectum, and permits the diffusion of its medicament into the surrounding tissues. Substances well absorbed from the rectum and therefore suitable for administration in the form of an enema or a suppository include:

The diffusible salts of sodium and potassium.
Alkaloidal salts.
The Digitalis glycosides.
Bromethol, Chloral hydrate, Paraldehyde, Pentobarbitone Sodium, Mersalyl.

Parenteral Administration of Drugs

Drugs are said to be parenterally administered when they are introduced directly into the tissues by injection through the integuments. It is, of course, essential that all substances so introduced, together with the apparatus employed in the operation, should be sterile.

Intradermal.—Intradermal injection is almost entirely confined to the introduction of test solutions as in the investigation of the origin of individual allergic reactions.

Hypodermic or Subcutaneous Injection.

This consists in the injection of a small bulk, not normally exceeding 1 mil of solution, into the fasciæ. Substances administered in this way include alkaloidal salts such as those of morphine and of strychnine, which are required to exert their full specific activity fairly rapidly. Most alkaloidal salts when given by mouth are absorbed somewhat slowly, and as detoxication commences with absorption, the maximal concentration obtained in the tissues represents only a fraction of the dose so administered. This disadvantage is overcome by parenteral administration.

Intramuscular Injection.

Since the muscles have an excellent blood supply and the fasciæ a relatively poor one, drugs injected into the muscles can diffuse more readily. Moreover, if by poor technique extraneous organisms are introduced with the injection, there is more chance of these being promptly dealt with by the protective mechanism of the body. Solutions of adrenaline intended to exert a systemic, as opposed to a purely local vasoconstrictor, effect are usually given intramuscularly. Another type of intramuscular injection is provided by "depot therapy." Insoluble salts are suspended in an aqueous or oily medium and injected deep into a muscle. In contact with the tissue fluids the metallic ions are gradually mobilised, so one injection will provide slow, continuous medication extending over several days. Examples of this are the official injections of bismuth salicylate and of calomel. Intramuscular injections of small bulk are usually put into the deltoid, and those of larger bulk into the gluteal muscles.

Intravenous Injections.

Since the substances so injected pass directly into the systemic circulation it is obvious that because of the risk of embolism the fluid injected must contain no solid material, or any substance which will react with the plasma to produce a precipitate. Nor must the injected substance be of a nature to cause hæmolysis. Strongly alkaline substances, and bodies like saponins which cause a marked lowering of surface tension, are dangerous in this respect. The advantages of intravenous injection are the rapidity with which the injected drug exerts its specific effect, and the absence of the great discomfort or pain which the intramuscular or subcutaneous injection of some drugs would cause. Examples of this are neoarsphenamine and iodophthalein. The latter is alkaline and intensely irritant, so that even intravenous injection must be slowly performed, and if any of the fluid is allowed to escape outside the vein at the site of injection, necrosis follows. In the case of some drugs the intravenous route is dangerous because the rapidity with which the action develops may spell disaster. Acetylcholine, for example, will inhibit the heart and cocaine paralyse the medullary centres. Strophanthin in acute cardiac crisis is excellent intravenously, but the initial and subsequent doses must be minimal, otherwise dangerous heart-block results.

Very large volumes, sometimes many litres, of various saline solutions, blood or plasma are administered by drip infusion. This procedure is often adopted following shock due to hæmorrhage, operations and injuries. In view of the large volumes of fluid employed, it is essential that these injections should not only be sterile, but free also from foreign protein in the shape of dead bacteria. These, so called "pyrogens," are usually the cause of the pyrexia and rigors which may follow large intravenous infusions.

Intrathecal (Intra-spinal injections).

Injections into the theca are made in the administration of spinal anæsthetics. Sometimes drugs are administered by this route in the treatment of meningeal infection. Injection is made between the lumbar vertebræ.

Intracardiac Injection.

Injection of sterile solution of adrenaline hydrochloride directly into the heart-muscle is made to remedy heart-block and to relieve cardiac arrest which may occur during prolonged anæsthesia, especially with chloroform.

Implantation.

This is more of a surgical procedure than injection. A small slit is made in a suitable muscle, the drug is implanted and the wound sutured. The drug acts as a depot from which the patient will derive mild continuous medication extending over many months. Tablets of desoxycorticosterone are not infrequently implanted in this way.

THE METALS

THE actions of the substances to be described under this heading are dependent on the following considerations: (*a*) the nature of the metal, (*b*) the solubility, concentration and degree of ionisation of the preparation. In other words, the true pharmacological action derives itself from the nature of the metal; the rest of the molecule acting as a contributory factor only in so far as it affects consideration (*b*) above. There are certain general points in regard to the metals which may be disposed of before proceeding to an individual review. The metal or its salts may be administered by mouth, in which case any benefit derived must result either from some corrective action within the tract or be exerted by the metallic ion after absorption. Parenteral administration of these substances is, where possible, made intravenously when prompt action is necessary, or by a depot in the muscle in order to spread the action over a long period, as the metal in the depot is gradually mobilised. Externally, the metallic salts differ in action, not only because of the varying properties of the individual elements, but also because of the factor of solubility. Freely soluble salts exert an immediate local effect, and may, if absorbed, exercise a remote effect (*e.g.* argyria); those slowly yielding therapeutically active ions may have a local action spread over a long period (*e.g.* zinc oxide), while other insoluble compounds may be used mainly for their protective effect on inflamed areas (*e.g.* kaolin).

In general, the ionising salts of the heavy metals in solution act as local astringents by precipitating the cell protein as metallic proteinate. This action results in the formation of a protective layer on the tissue surface which hinders the absorption of toxins. Moreover the penetration of the metallic ion is self-limited by this coagulum. Even in high dilution (of the order of one in a million) a mild bacteriostatic action may be exerted, and in more concentrated solution salts of many metals are bactericidal by coagulating the bacterial protein. This process is hindered, although not completely inhibited, by the presence of organic matter. In the case of mercurial salts this inhibition is due to absorption of the metal by organic matter, while silver salts tend to be largely inactivated by precipitation by chloride in tissue fluid. On account of these astringent and antiseptic properties, weak solutions of soluble salts, especially of silver, zinc and copper, are of value in the treatment of inflammations of the conjunctiva, urethra, bladder and colon; given orally they exert an emetic effect by irritating the stomach. In concentrated solution, or solid form, soluble salts of some of the metals (*e.g.* silver) are corrosive.

When taken by mouth, absorption is slow but excretion is slower, so cumulation, particularly in the liver, is prone to occur. This is common in the case of lead and mercury, but rare with zinc and copper. They are excreted by the colon, kidneys and salivary glands and set up irritation, and their toxic action is mainly on the nervous system, alimentary tract and kidneys. Individual metals (*e.g.* arsenic) are efficient chemotherapeutic agents within the tissues; some of these are separately considered, but the present chapter contains a cross-reference to them. Although, for various reasons, organic salts of some of the metals are most suitable for specific therapeutic purposes, the inorganic salts, being more readily ionised, have a considerably higher potency.

Aluminium

The soluble salts of aluminium are mildly antiseptic and astringent, but non-corrosive and comparatively non-toxic. Externally a 25% solution of aluminium chloride is used to deodorise and check excessive perspiration, especially from the axillæ, while a solution of aluminium acetate (Burow's Solution) forms a useful cooling lotion for local œdema, bruises, strains, gnat-bites, etc. The alums, soluble double salts of the general formula $R_2SO_4.Al_2(SO_4)_3.24H_2O$, are used in solid form as styptics; in solution they are applied to the mucous membrane of the mouth, usually as Glycerin of Alum, while for irrigation of the urethra and vagina a 1% solution of the salt may be employed.

Canadian investigators report that aluminium is of value in the prophylaxis and treatment of silicosis.

Aluminii Hydroxidum, 5–10 gr.

This is prescribed as a gastric antacid. A colloidal form of aluminium hydroxide is widely advocated in the treatment of peptic ulcer; the dosage advised being 60 to 180 gr. one hour after meals. It can also be given by intragastric drip. It has some neutralising action on gastric juice but its main action is by physical adsorption of peptic acid.

Aluminii Subacetas (*vide* Anthelmintics).

Aluminium Phosphate.

This salt, used as a gel, has recently been employed as an antacid. It is prepared as a 4% suspension and given in doses of 1 fl. oz. The gel, diluted 1 in 3, can be given by intranasal drip at the rate of 15 drops per minute.

Basic Aluminium Aminoacetate.

This is a recently introduced antacid compound. The amino group effects immediate neutralisation of gastric HCl and this is followed by the buffering action of the aluminium salt.

Aluminium sodium silicate is used as an antacid.

Kaolinum, ℥ſs–℥ii.

Kaolin is a naturally occurring silicate of aluminium. The official, purified product is administered internally as an adsorbent of toxins and as a substitute for bismuth carbonate. It is employed against enteritis and colitis due to cholera, dysentery, food-poisoning, and other infective diarrhœas. For external use as an adsorbent dusting powder for septic wounds, ulcers, etc., kaolin must be sterilised by dry heat at 150° C. for one hour to kill tetanus spores which may be present, as in any natural earth.

Cataplasma Kaolini, Off. (Kaolin poultice, *Antiphlogistine,** sim.).

This is a paste massed with glycerin and containing volatile oils, etc., which is applied hot to promote an active local circulation and relieve pain in pneumonia, arthritis, etc., and for small contaminated wounds. The dressing of hot poultice is usually applied on lint and covered with cotton-wool.

Glycerinum Aluminis, Off. (Glycerin of Alum).

An astringent application, especially for mucous surfaces.

Antimonium (*q.v.*)

Argentum

(Silver)

Argenti Nitras, ⅛–¼ gr.

Silver nitrate is employed as a caustic stick (*Argenti Nitras Induratus*, Off.) to ulcers and to destroy warts. In dilute solution (1 : 10,000) the salt is used as an astringent antiseptic, and a stimulant to granulation. Solutions of 1% are used as eye drops to prevent *Ophthalmia neonatorum*,[1] and from 0·1%–1% for lavage in ulcerative colitis. For bladder irrigation and urethral and vaginal injection, strengths from 1 : 20,000–1 : 5,000 or stronger are used progressively. Eczema of the flexures is well treated with a 2% solution, or by the following paint:

℞ Argent. Nit. .. .. gr. xvi
Sp. Æther. Nit. .. .. ad ℥i
ft. pigment.

10 minims of 5% solution can be injected into the pleural cavity in recurrent spontaneous pneumothorax to promote the formation of fibrin and so seal the leak; also before thoracoplasty operation to obliterate the pleural cavity.

Silver nitrate has been given orally in pill form, for ulceration of the alimentary tract, but incurable skin pigmentation (*argyria*) may result.

Argentoproteinum, Off. (*Protargol*,* Strong Silver Proteinate).

This compound of silver and protein is used to replace silver nitrate as a local antiseptic. Owing to its feeble ionisation it is far less irritant than the nitrate and almost non-astringent, but the germicidal action is much inferior to that of the nitrate. For application to the eyes, the nose and throat, solutions from 2%–10% are employed; the same strength is used, also, for urethral injection in chronic gonorrhœa. A 1% solution is used for colonic lavage in ulcerative colitis. Ointments containing 2%–10% in soft paraffin are used for the eyes.

Argenti Proteinas Mite (*Argyrol**).

This compound is of a similar character to the above but it contains a considerably smaller proportion of *ionisable* silver. Its indications are similar to those of Argentoprotein.

Colloidal Silver (*Collosol Argentum**).

This contains a 0·05% colloidal suspension of silver. Its indications are similar to those mentioned for the other silver preparations.

Arsenum (*q.v.*)

Aurum

(Gold)

Auri et Sodii Thiosulphas (*Novacrysin*,* *Sanocrysine*,* *Crisalbine**).

Sodium aurithiosulphate is used intravenously in the treatment of pulmonary tuberculosis, *lupus erythematosus* and rheumatoid arthritis in progressive dosage.

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[1] But may cause acute conjunctivitis, which is best remedied by one drop of liquid paraffin in each eye.

It is usual to give a series of doses commencing with 0·01 G. and gradually working up to a maximum of 0·1 G. at five- to seven-day intervals. The total course should be limited to 1 gm. but may be repeated at intervals of about 6 months. Larger doses are sometimes used, particularly in phthisis, but complications such as fever, dermatitis, stomatitis, albuminuria, purpura, agranulocytosis and liver damage have occurred. Nervous complications including restlessness, confusion, aphasia, hemiparesis, cranial nerve palsies, herpes zoster and polyneuritis may occur. Gold is thought to have a specific action on the tubercle bacillus, but its use in other conditions is largely empirical. It has proved of some benefit in the treatment of leprosy, especially in the ocular complications of the disease. A suspension of the salt in oil for intramuscular injection is available commercially in varying strengths; this is sometimes preferred, as being less liable to precipitate acute reaction to the drug. For the treatment of the toxic symptoms, see liver, calcium thiosulphate and ascorbic acid. Dimercaprol or BAL (British Anti-Lewisite), referred to in the treatment of mercury and of arsenic poisoning, may also be of value here and following its use there is an increased urinary excretion of gold. BAL may cause inflammation at the site of injection, generalised pains, nausea, vomiting, sweating, salivation and lachrymation.[1] Less toxic derivatives of BAL, now available, may prove advantageous.

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Other organic compounds of gold are available; their indications are similar to those of sodium aurithiosulphate. Such compounds are aurothioglucose (*Solganol B** and *Solganol B oleosum**) and sodium aurothiomalate (*Myocrisin**). Calcium aurothiomalate (*Aurocalcium**) is said to be less toxic than the sodium salt. Colloidal gold is employed in Lange's colloidal gold test of the cerebrospinal fluid.

Barium

The soluble salts of barium (including the carbonate, which is soluble in the gastric acid) are powerful corrosive poisons. They exert a marked stimulating action on muscle but are seldom employed therapeutically.

Barii Chloridum, ½–1 gr.

Barium chloride given by mouth, well diluted, four times a day will sometimes prevent the symptoms (Stokes-Adams's Syndrome) due to complete heart-block.

Barii Sulphidum.

Barium sulphide mixed with starch or other diluent, and made into a paste with water, is applied to remove hair in hypertrichosis. After a few minutes the paste is scraped off gently with a blunt knife and the part swabbed with warm water and dried with the aid of a dusting-powder to minimise risk of dermatitis. The active solvent agent is hydrogen sulphide, which is slowly evolved by hydrolysis of the barium sulphide when it is mixed with water. The powder may be used to remove keratotic patches in ringworm, but it is irritant.

Barii Sulphas.

Barium is opaque to X-rays, and since barium sulphate is insoluble in the digestive juices, it is non-toxic and forms a valuable contrast medium for radiography of the stomach and intestine.

Enema Barii Sulphatis, B.P.C. (*Benema*,* sim.).

Pulvis Barii Sulphatis Compositus, B.P.C. (Barium Meal).

Bismuthum

Various salts of bismuth are employed parenterally as chemotherapeutic agents in the treatment of syphilis. For this purpose it is common to use an aqueous or oily suspension of a suitable salt which is injected intramuscularly at weekly intervals concurrently with arsenical medication. Watery suspensions such as the official injection of bismuth oxychloride are more rapidly absorbed than oily ones, *e.g.* bismuth salicylate injection.

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[1] Fixation of calcium ions may cause latent tetany.

Absorption from these depots is very slow, and affords mild continuous medication which may last over many months. Bismuth is therefore of value in maintaining an antispirochætal action in the tissues in between the injections of arsenic, because although the latter is more active, it is also excreted more rapidly. The advantages of bismuth over parenteral mercurial preparations in syphilis are that they are more effective, less painful and less toxic to the kidneys. Bismuth lies midway between the organic arsenicals and mercury in its toxicity, and the symptoms are similar to those produced by mercury, viz. blue line on gums, stomatitis, albuminuria, diarrhœa. The superiority of bismuth over organic arsenic is that it is less liable to cause dermatitis or damage to the liver. The weekly dose equivalent to 0·2–0·24 gm. of metallic bismuth, is given for 10 weeks. Further courses are given at intervals of 4–6 weeks.

Bismuth preparations are sometimes used in the treatment of rheumatoid arthritis. They are less toxic but not so effective as the gold salts and should be reserved for gold-sensitive patients. A course of 2 gm., spread over weekly intervals, is recommended (see sodium bismuthyl tartrate, p. 10).

Injectio Bismuthi, Off. (*Bisglucol**), 8–15 min.

An aqueous suspension of precipitated bismuth for intramuscular use in the treatment of syphilis. The suspension is made up in isotonic glucose and contains 0·2 gm. per mil. Suspensions of bismuth oxychloride or bismuth salicylate are usually considered to be superior.

Quinine Iodobismuthate (*Quinostab**).

This is prepared as an oily injection for intramuscular use in syphilis, particularly for cardiovascular and neurosyphilis. It contains the equivalent of 0·02 gm. of metallic bismuth per mil. Its action is more rapid than that of the insoluble bismuth salts, but more prolonged than in the case of the soluble sodium bismuthyltartrate. The dose recommended of the 10% suspension is 3 ml. twice weekly for 20 doses.

Bismuthi Carbonas, 10–30 gr.

Externally, bismuth carbonate is occasionally employed as a dusting powder in exudative dermatitis and for small ulcers; it exerts a protective and adsorptive action. Internally it is commonly given before food to protect a peptic ulcer or inflamed *mucosa* and to check diarrhœa. It may diminish the absorption of toxins and exert a mild astringent effect, but modern clinical evidence rather controverts former theories as to its value as a protective to ulcers, etc. It is usually administered with sodium bicarbonate as a component of antacid powders (see chapter on Alkalis). Bismuth carbonate is still occasionally used as a contrast medium in radiography of the intestine, etc., it is said to produce a denser shadow than barium sulphate. The salt finds occasional use, also, as an ingredient of medicated insufflations for the nose.

Bismuth Hydroxide (*Casbis**, *Muthanol**).

Is used in the treatment of syphilis as an oily suspension containing the equivalent of 0·08 gm. metallic bismuth per mil.

Bismuthi Oxychloridum, 10–30 gr.

This is given internally for the same purposes as bismuth carbonate; in mixture form it is incompatible with sodium bicarbonate. It is employed by intramuscular injection in syphilis and has largely replaced mercurial injections.

Injectio Bismuthi Oxychloridi, Off. (*Bisoxyl**), 15–30 min.

An aqueous suspension of the salt for intramuscular injection. It contains the equivalent of 0·08 gm. metallic bismuth per mil.

Bismuthi Salicylas, 10–30 gr.

Bismuth salicylate is slowly hydrolysed in the intestine with the formation of bismuth carbonate and of sodium salicylate. It exerts, therefore, a mildly antiseptic as well as an adsorptive action, and it is used in colitis, etc. Except as a dry powder it is incompatible with sodium bicarbonate.

As an intestinal antiseptic:

℞ Bismuthi Salicyl.
Carbo. Ligni } .. .. āā gr. v
Betanaphthol. .. .. gr. ii
ft. oblatum.

The salt is used suspended in oil as an intramuscular injection in syphilis.

Injectio Bismuthi Salicylatis, Off. (*Bisantol,* Bismosan**), 10–20 min.

An oily suspension for intramuscular injection. It contains the equivalent of 0·06 gm. metallic bismuth per mil.

Bismuthi Subgallas (*Dermatol**), 10–30 gr.

Bismuth subgallate occurs as a minutely subdivided, yellow powder, insoluble in water. It has mild adsorbent and antiseptic properties, and is used externally as a desiccant dusting-powder, and orally or rectally, in aqueous suspension, in the treatment of diarrhœa, particularly in ulcerative colitis.

Bismuthi Subnitras, 5–20 gr.

Bismuth subnitrate is similar in action and uses to bismuth oxychloride. Combined with iodoform (*q.v.*) as "B.I.P.P." it is used for septic wounds.

Bismuthi et Sodii Tartras, 1–3 gr. (by injection).

Sodium bismuthyltartrate is a freely soluble preparation used occasionally by intramuscular injection in the treatment of syphilis. Depot injection with a slowly mobilised salt of bismuth is, however, more favoured in modern therapy. It is claimed to be effective in rheumatoid arthritis in doses of ½ to 1 gr., injections being given at intervals of a week or less frequently.

Injectio Bismuthi et Sodii Tartras, *Off.*

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Oily solutions soluble in body lipoids are *Bivantol,* Cardyl,* Neocardyl,* Stabismol,* Lipobismol.** The weekly dose is given in two injections because of their low bismuth content (0·03 to 0·05 gm. per mil.) and their more rapid absorption and excretion. Lipobismol (bismuth octyl-oxyacetate) contains the equivalent of 0·1 gm. of bismuth metal per mil. *Thio-Bismol** (sodium bismuth thioglycollate) is a water-soluble preparation. Apart from its use in syphilis it is said to be effective in controlling therapeutic malaria. Two injections of 0·2 gm. are given weekly.

Calcium [1]

In addition to its rôle in bone formation, the calcium ion plays a varied and important part in the restoration and maintenance of physiological processes. It increases the force of the heart's beat and prevents undue excitability of the motor nerves. Calcium ion deficiency in the tissues, resulting in undue motor irritability with the manifestations of tetany, can be brought about by (1) alkalosis, which depresses the ionisation of the calcium salts, (2) by removal of the parathyroid (*q.v.*) glands (*e.g.* after thyroidectomy), and (3) by defective calcium adsorption due to vitamin D (*q.v.*) deficiency. Tetany due to alkalosis can be relieved by ammonium chloride or calcium chloride, and if associated with low blood chloride and high blood bicarbonate (*e.g.* after the prolonged vomiting of pyloric stenosis or high intestinal obstruction) the condition will require, in addition, intravenous sodium chloride. If large doses of alkalis are being taken as in the treatment of peptic ulcer, these must be discontinued. Tetany from other causes is remedied by intravenous injection of an ionisable calcium salt and the administration of parathyroid extract to mobilise calcium from the bones. The administration of vitamin D concentrates is necessary if the condition is due to deficiency of this vitamin. During pregnancy, the demands of the growing fœtus deplete the maternal supplies of calcium; this can be met by the oral administration of a suitable calcium preparation to the mother. Calcium diminishes the permeability of capillary endothelium and may increase the coagulability of the blood, and it is commonly prescribed in conditions thought to be associated with increased capillary permeability, or a tendency to hæmorrhage such as purpura, chilblains, serum sickness, urticaria and hay-fever. It is also administered in tuberculosis to aid in healing. The evidence of real benefit in these conditions is, however, very uncertain. The administration of calcium after hæmorrhage may be of value since it has been shown experimentally that calcium helps to conserve iron. Liver necrosis, as may arise from carbon tetrachloride therapy, may partly be prevented and controlled by the intravenous use of a calcium salt, possibly by decreasing the permeability of the cell membranes. Calcium is administered following the parathyroid treatment of lead-poisoning. The parathyroid is given to mobilise lead which has been deposited in the bones, but it removes, also, some of the calcium so resulting in a deficiency which requires correction. Finally, the twitchings of uræmia, which are associated with deficiency of calcium ion in the cerebrospinal fluid, can be remedied temporarily by giving a calcium salt intravenously.

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[1] Normal calcium requirements are 0·45 gm. daily, but are doubled in children and during pregnancy. Milk, cheese and eggs are the most important sources.

Calcii Carbonas (*q.v.*).

Calcii Chloridum Hydratum, Off. Intravenous, 10–30 gr.

This is better absorbed from the intestine than other salts of calcium, but it is nauseous, and irritant to the stomach and should be avoided for oral use. Intravenously (5%–10% solutions), it is given in all conditions where calcium is desirable, but it is liable to cause acidosis (*v.* general salt action). On account of this action it is administered intravenously to overcome alkalosis arising from hyperemesis, etc.

Calcii et Sodii Lactas, 5–30 gr. (*Kalzana**).

Calcium sodium lactate is not so readily absorbed from the intestine as calcium chloride, but it is non-irritant and does not produce acidosis. It is used orally, often in conjunction with vitamin D.

Calcii Gluconas, 30–60 gr. (*Calcium Sandoz**).

This salt is given orally, and specially prepared solutions containing 5%–10% may be injected subcutaneously into the muscle (calcium depôt), or intravenously when calcium therapy is indicated. Calcium lævulinate possesses similar properties.

Calcii Hydroxidum, 5–15 gr.

Mixed to a thin suspension in water, calcium hydroxide is used against oxalic acid poisoning. As the dilute *Liquor Calcii Hydroxidi* (Lime Water), 1–4 fl. oz., it is added to the milk feeds of infants.

Calcii Lactas, 15–60 gr.

This has the same properties as the double salt with sodium, but is less readily absorbed from the gut.

Calcium Oleate.

A 0·85% colloidal solution of calcium oleate (*Collosol Calcium**) can be employed in conditions where calcium is indicated and is given by mouth or intramuscular injection.

Calcii Sulphas Exsiccatus, B.P.C.

Plaster of Paris occurs as a white odourless powder. When admixed with a little water it hydrates and quickly sets to a hard mass. It is used in plaster bandages and for making casts for dental and general surgical purposes.

Calcium Thiosulphate (*Calciostab**).

This substance and a similar compound sodium thiosulphate (*Thiostab**) are used in the treatment of poisoning by metals such as arsenic, gold, bismuth, and are mainly of value for the dermatitis and stomatitis occurring in these conditions. They are usually given intravenously in doses of 0·5 to 1 gm., but may also be used orally in doses of 10 gr. The sodium compound may be given intravenously in doses of 10 to 50 mil. of a 20% solution for cyanide poisoning. As a lotion it is used in ringworm and scabies, the concentration being 10% for the former and 40% for the latter.

Cuprum

The soluble salts of copper exert an antiseptic action and are astringent by the precipitation of protein. They stimulate the granulation of healthy tissue and are used to heal ulcers of the mucosa and skin. A trace of copper given concurrently with iron is said to increase the production of hæmoglobin. The copper ion has been stated to be specific in the treatment of trachoma. Copper salts have been used in the treatment of rheumatoid arthritis; sodium cupro-allyl-thio-urea-benzoate has been injected intravenously, beginning with 0·1 gm. and increasing to 0·25 gm., a course consisting of 2–5 gm.

Cupri Sulphas, ¼–2 gr.; emetic, 5–10 gr.

Copper sulphate is occasionally used as an emetic. It is specific for phosphorus poisoning since it fixes the phosphorus as insoluble copper phosphide. For external phosphorus burns a 1% solution is employed. Solutions 0·25–0·5% may be applied to the eyes in conjunctivitis and

0·5–1% for application to discharging gums. Recently, iontophoresis with 1% copper sulphate has proved a useful method for treating ringworm of the feet.

Cupri Oleas.

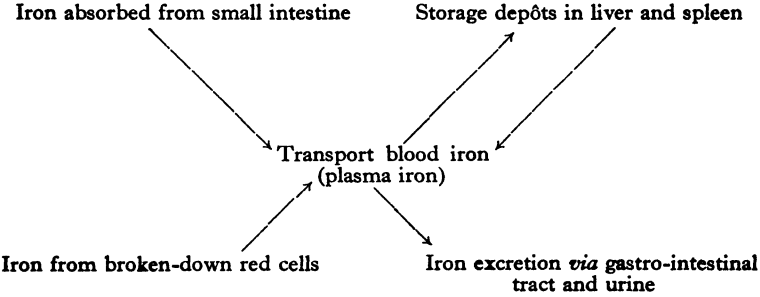
A 12·5% ointment is employed in the treatment of ringworm, warts and corns.

Ferrum

Iron is necessary to hæmoglobin formation. In health the iron content of the adult body is about 3 grammes and that lost by excretion needs replacement by iron from ingested foodstuffs at the rate of 15 mg. daily for women and children, and 5 mg. for men. During pregnancy 20 mg. or more are required.[1] After absorption, the iron passes to the bone marrow, where it is conjugated with protoporphyrin type III and protein to form hæmoglobin. Plasma iron (70–180 γ per 100 ml.) is derived as follows:

1. Absorption from the alimentary tract.
2. From destroyed red cells.
3. From storage depôts in the liver and spleen.

According to the current requirements of the organism, iron leaves the plasma either to participate in hæmoglobin formation in the red bone marrow as indicated above, or to be stored in depôts. Any excess over the amounts so utilised is excreted. The following diagram (after Moore, Doan and Arrowsmith) illustrates the continuing process:


Iron absorbed from small intestine
Storage depôts in liver and spleen
Transport blood iron (plasma iron)
Iron from broken-down red cells
Iron excretion *via* gastro-intestinal tract and urine

The amount of iron absorbed from the alimentary tract increases if the storage depôts are depleted, *e.g.* in anæmia. The bulk of the absorbed iron is converted into hæmoglobin within a week and very little goes into the storage depôts except in infective states.

Iron therapy is used specifically in the hypochromic anæmias, *i.e.* the nutritional anæmia of infants, idiopathic hypochromic anæmia and the hypochromic anæmia of pregnancy, chlorosis, after severe hæmorrhages and infections. About 25 mg. of iron must be absorbed to make good each 1% of hæmoglobin deficiency in anæmia. Traces of certain other metals, especially copper, activate iron in the formation of hæmoglobin. Preparations of iron are used empirically for their supposed "tonic" effect in many conditions of ill-health. It is an orthodox theory that the essential feature of iron therapy is the supply of an adequacy of ferrous ions to the small intestine. This can be accomplished best by administering the soluble frerous sulphate or ferrous chloride after meals to minimise gastric irritation and any constipating astringent action. Iron preparations which are insoluble in water—Blaud's Pill, ferrous phosphate, reduced iron, etc.—pass into solution in the stomach, granted a sufficiency of peptic acid. Ferric iron, such as is present in the scale preparations (iron ammonium citrate, etc.), is probably absorbed only to the extent to which the colloidal nature of the compound is broken down and the iron reduced to the ferrous state. This may account for the very large dosage of the scale preparation required in intensive iron therapy, in comparison with the soluble, inorganic, ferrous salts. Very large doses in small children have caused severe gastric irritation, liver damage and even death. When iron by mouth disagrees, the intramuscular injection of a suitable compound may be employed, but there is evidence of kidney damage ensuing in some cases. The intravenous administration of iron preparations has previously been found impossible because precipitation of iron in the blood leads to toxic symptoms due to minute emboli. A recent claim is made that saccharated iron oxide (B.P.C.) can be so administered without severe reactions. Five hundred mg. given as a ·1 to 1% solution in 5% dextrose has been found effective. This work, if confirmed, may prove of value in iron deficiency anæmias with grossly impaired powers of alimentary absorption. However administered, iron is excreted very largely into the large intestine and it turns the stools black by the formation of sulphide. Similarly blackening of the teeth and the tongue may occur, also as a result of sulphide formation. Externally, soluble salts, especially ferric chloride and iron alum, exert a powerful styptic action by protein precipitation.

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[1] Iron-containing foods are oatmeal, wholemeal bread, liver, pulses, green vegetables, red meat, dried figs and apricots, cocoa.

Ferri et Ammonii Citras, 20–40 gr.

A "scale" preparation of ferric iron, so called because it is prepared in the form of irregular platelets reddish-brown in colour. Relatively non-irritating and non-astringent, because the iron is in the colloidal state, it is best prescribed in mixture form.

The following mixture is suitable when an aperient is required also:

℞	Ferri et Ammon. Cit. ..	gr. xx
	Elixir Cascaræ Sagrad. ..	♏xv
	Aq. Chloroformi	ad ℥ſs
	ft. mist.	pro dos.

Ferri et Sodii Citras (*Naferon**).

Is neutral in reaction and non-irritant. It is administered in 7½ gr. capsules.

Ferri Carbonas Saccharatus, Off. 10–30 gr.

This contains ferrous carbonate partly stabilised with glucose. It is often used, suspended in mixture form, for children.

Ferrum Redactum, 1–10 gr.

Reduced iron may be prescribed in pill or tablet form or, for children, it may be sprinkled over bread and butter.

Ferri Sulphas, 1–5 gr.

Ferrous sulphate is suitable for administration in pill, tablet or mixture form. Mixtures should contain a small dose of sulphuric acid to retard oxidation of the iron. For an adult, a daily dosage of 20 gr. will usually suffice to remedy hypochromic anæmias, and 30 gr. daily will raise the daily hæmoglobin by about 4%.

A suitable mixture is:

℞	Ferri Sulph.	gr. v
	Mag. Sulph.	gr. xx
	Acid. Sulph. Dil.	♏x
	Glycerini	ʒſs
	Aq. Chloroformi	ad ℥i
	ft. mist.	pro dos.

Ferrous sulphate in enteric coated tablets (*e.g. Enseals,** Ferrous Sulphate, Eli Lilly) is sometimes used when the salt, alone, is too irritant to the alimentary tract.

Pilula Aloes et Ferri, Off. 4–8 gr.

May be prescribed when iron and an aperient are required; also for functional amenorrhœa.

Pilula Ferri Carbonatis, Off. (Blaud's Pill), 5–30 gr.

It is important to bear in mind that ferrous carbonate, as such, is not diffusible from the intestine. An adequacy of peptic acid is necessary to convert it into the soluble ferrous chloride before absorption can occur. This applies to all the water-insoluble preparations of iron.

Syrupus Ferri Iodidi, Off. ½–2 fl. dr.

Syrupus Ferri Phosphatis Compositus, Off. ½–2 fl. dr. (" Chemical Food ").

An agreeable, acidulated syrup suitable for children. It contains ferrous phosphate with free phosphoric acid, calcium phosphate and a little of the phosphates of sodium and potassium.

Syrupus Ferri Phosphatis cum Quinina et Strychnina, ½–1 fl. dr. (Easton's Syrup).

This is used as a general " tonic," especially during convalescence.

Ferrodic.*

Contains ferrous phosphate and a trace of copper stabilised with dextrose and flavoured with chocolate. It is prepared in the form of granules, which are usually acceptable to children who may reject other forms of iron. One drachm of the granules is equivalent to 20 gr. of Blaud's Pill.

Liquor Ferri Dialysatus (B.P.C.) (*Colliron,* Collosol Ferrum**).

This is a colloidal solution of ferric hydroxide and is used in doses of 10 to 30 minims in the treatment of anæmia. One-ounce doses repeated frequently are used as an antidote in arsenic poisoning (*q.v.*).

Hydrargyrum (*q.v.*)

Lithium

Certain salts of lithium, notably the carbonate and citrate, are occasionally used as diuretics. They render the urine alkaline, and were formerly supposed to exert a solvent action *in vivo* on urates deposited in the tissues. Lithium salicylate in 35% aqueous solution is employed as a sclerosing agent for varicose veins.

Magnesium, *vide* Magnesii Sulphas. Antacids

Pure talc, a hydrated magnesium silicate, is used as a dusting powder. Its presence on rubber gloves may result in the contamination of the peritoneal cavity at operation with subsequent adhesions.

Manganum (Manganese)

Preparations of manganese are used sometimes in the hope of stimulating antibody formation by the tissues.

Mangani Butyras (*Collosol Manganese*,* sim.).

Manganese butyrate may be used intramuscularly; 15–30 minims of a 1% solution may be injected at five-day intervals, with a maximum of three injections, in the treatment of staphylococcal and resistent gonococcal infections. It has been almost completely replaced, however, by penicillin or sulphonamide (*q.v.*) therapy.

Plumbum (Lead)

The salts of lead are used for their astringent action on the skin and, formerly, on the alimentary tract. An insoluble albuminate of the metal is formed and serves as a protective coagulum which prevents further penetration of the metallic ions. Since, however, the excretion of lead is very slow, lead-poisoning may result from continued dosage, or arise as an occupational disease among lead workers and painters. Overdosage is evidenced by motor neuritis, spasm of smooth muscle, gout, a blue line on the gums, chronic nephritis and hypertension, intestinal colic, cerebral symptoms (lead encephalopathy and convulsions) and anæmia with a typical blood-picture showing stippled basophils. In pregnancy, short-term abortion may result.

Plumbi Acetas, ½–2 gr.

Lead acetate is now rarely used internally.

The official dilute solution of lead subacetate is used externally as an evaporating lotion to soothe and reduce local œdema, and to relieve itching.

Liquor Plumbi Subacetatis Dilutus, Off.

Pilula Plumbi cum Opio, B.P.C. (dose: 1 or 2 pills).

Suppositorium Plumbi cum Opio, Off.

This is prescribed occasionally to check bleeding from piles; the opium alkaloids may help to relieve the pain after absorption.

Plumbi Oleas.

Lead oleate is mildly astringent and soothing to inflamed surfaces when used in ointment form. It forms the basis of the official lead plaster.

Unguentum Plumbi Oleatis, B.P.C.

Potassium (*v.* Salt Action)

The salts of potassium are better diffused from the alimentary tract than the corresponding salts of sodium. The K-ion has a lower renal threshold than the Na-ion and is, therefore, more diuretic. In toxic concentrations it arrests the heart in diastole. A low serum potassium level can occur: (1) in alkalosis; (2) associated with the paralytic attacks in family periodic paralysis and chronic nephritis; (3) after testosterone and D.O.C.A. therapy. The paralysis in group (2) can be relieved by 1·5 g. of potassium chloride intravenously. Recent evidence suggests that there may be deficiency in gastro-enteritis in infants which may be corrected by adding potassium chloride to the other fluids administered parenterally.

Stannum

Preparations of tin have been claimed to exert a beneficial effect in some cases of staphylococcal infection. The following formula is prescribed for oral administration in cases of boils, carbuncles, and postular acne. It is more effective when yeast (*q.v.*) is administered concurrently:

Tabella Stanni Co. N.F. (*Stannoxyl,** sim.) .. 1–3 pro dos.

(Each tablet contains approximately 1¾ gr. of powdered metallic tin and ⅛ gr. of stannous oxide.)

Thallium

Thallium Acetate.

This drug has been given orally in doses of 8 mg. per kilo. bodyweight as a depilatory agent in ringworm of the scalp. It may cause toxic effects such as gastro-intestinal upset and joint pains, and fatalities have occurred from overdosage. It has largely been superseded by X-ray therapy.

Zincum

The salts of zinc are astringent and caustic like those of copper and silver, but inferior to them in antiseptic properties. Various preparations of zinc, notably the oxide and the valerianate, have been administered internally to check the night-sweats of phthisis and as sedatives to the central nervous system, but their beneficial action is very dubious.

Calamina.

Calamine is zinc carbonate usually containing some oxide of zinc and iron. It is used as a dusting-powder, mixed with starch, etc., and as a lotion to exert a protective, astringent and sedative action on inflamed and irritable skin areas.

Oily preparations containing calamine are used to protect the skin from sunburn and to relieve dermatitis, especially that produced by insolation or excessive actinotherapy.

Lotio Calaminæ, B.P.C.

This lotion is applied as a mild astringent to the skin in many types of dermatitis.

In cases where calamine lotion is too "drying" to the skin, the addition of 10% of liquid paraffin is a distinct advantage. The preparation resulting is not a completely oily product like calamine liniment but contains enough oil to mitigate the desiccant action of the zinc ions.

Linimentum Calaminæ, B.P.C.

This is a typical oily preparation of calamine widely used in dermatology. To it may be added 2%–4% of menthol or of camphor to relieve pruritus or pain (*e.g.* in *herpes zoster*). For the treatment of acute eczema, seborrhœic dermatitis, etc., 2%–5% of ichthammol (*q.v.*) is a useful addition.

Zinci Chloridum.

Zinc chloride is a powerful caustic and its solutions are highly astringent and antiseptic. The following strengths of aqueous solution may be employed for the purposes named:

2%	For application to fœtid ulcers.
1%–2%	As a wound-dressing; free drainage being maintained.
0·5%	For use in the axillæ as a deodorant.
1 : 1,500	For urethral and vaginal irrigation. A similar strength has been applied to septic gums and tonsils, but it is apt to promote the growth of fibrous tissue.

Zinci Oxidum.

Zinc oxide has a wide range of utility in the local treatment of dermatoses. It is employed in the form of dusting powder, ointment and lotion, and it is mildly astringent, relieves irritation and protects slightly abraded surfaces.

Cremor Zinci, B.P.C.

Gelatinum Zinci (Unna's Paste), Off.

Zinc oxide in a glycerin-gelatin base which is applied molten and allowed to set to form a flexible, protective and mildly astringent application, especially for eczematous patches.

Pasta Zinci Oxidi Composita (Zinc Paste), Off.

Pasta Zinci Oxidi cum Acido Salicylico, B.P.C. (Lassar's Paste).

This preparation is widely used as an application in subacute and chronic dermatitis, it reduces irritation and promotes healing. In the treatment of inflammatory conditions such as impetigo it is now common to add 5–10% of a sulphonamide to Lassar's paste, but sulphonamide sensitivity may be induced (*q.v.*).

Pulvis Zinci et Acidi Borici, B.P.C.

Pulvis Zinci et Amyli, B.P.C.

The two foregoing dusting-powders are mildly astringent and absorbent. The former is used mostly as a foot powder and for intertrigo, and the latter as a desiccant in exudative conditions of the skin. In intertrigo, the addition of 20% of talc and 5% of light magnesium carbonate to neutralise perspiration, which becomes acid on decomposition and is then highly irritant to chafed patches, greatly increases the practical utility of the B.P.C. powder.

Unguentum Zinci et Olei Ricini, B.P.C. (Carling's Ointment).

This ointment is used chiefly as an application for sore buttocks in infants. Admixed with 0·1% of scarlet red (*q.v.*) it promotes the healing of bed-sores.

Unguentum Zinci Oxidi, B.P.C. (Unguentum Zinci).

Zinci Peroxidum (*q.v.*).

Zinci Stearas.

Zinc stearate is used as a soothing and mildly astringent and antiseptic dusting-powder in acne, eczema, intertrigo, etc. Zinc oleostearate is used similarly.

Zinci Sulphas, 1–3 gr.; emetic, 10–30 gr.

Zinc sulphate is now rarely used internally even as an emetic. Lotions containing various proportions of zinc sulphate are used externally to stimulate the granulation of indolent ulcers, for their astringent effect in conjunctivitis and for urethral and vaginal irrigation. For the last-mentioned purpose a 1 : 500 solution is commonly employed. Zinc sulphate being less ionised in solution is not nearly so corrosive as zinc chloride.

Collyrium Acidi Borici et Zinci, B.P.C.

This is a very commonly prescribed astringent and antiseptic eye lotion.

Lotio Rubra.

Red lotion is commonly used in hospital practice for indolent ulcers. It contains zinc sulphate and is coloured.

Radioactive Metals

Radium, uranium and thorium are the important radioactive metals, undergoing gradual disintegration as the result of the disintegration of their atoms and the liberation of ionising radiations in the process. In the case of radium these radiations are (1) alpha particles (helium nuclei), (2) beta rays (electrons), and (3) gamma rays, these radiations being destructive to tissues, particularly rapidly proliferating ones, such as those of malignant disease. The gamma rays are therapeutically of great value, particularly in malignant disease, as they are able to penetrate tissues and are similar in character to roentgen rays. The external application of radium may cause dermatitis, burns and even skin cancer, and may also cause constitutional symptoms such as toxæmia, blood dyscrasias and sterility.

Radium and radioactive compounds, when used in industry (mining radioactive ores, etc.) and in non-ethical medicinal preparations, can occasionally cause poisoning due to ingestion and absorption. The alpha particles are particularly dangerous, as they are destructive to bone and cause decalcification with spontaneous fractures, as well as a terminal aplastic anæmia.

Radioactive Isotopes.

Radioactive isotopes of common elements are formed by various modern methods involving atomic fission. The radioactive isotopes can be formed by bombardment with nuclear particles. This can be done in a cyclotron, or in a graphite pile; in the latter case the yield is higher. They have the following uses: (1) **Tracers.**—Radioactive NaCl is used to determine the rate of diffusion by the blood stream and to measure lymph volume of certain organs. Radioactive iron is employed to determine the unit volume of blood in the investigation of surgical shock. It has two isotopes which can be detected, and this enables the relative survival of fresh and stored blood in the blood stream to be determined. It has also been discovered by the use of iron isotopes that iron from hæmolysed blood is taken up by new cells in preference to that supplied by even large amounts of iron given from without. Tracer methods have enabled observations to be made on metabolism of chemical substances within the cells. They are also used in cancer research, and radioactive phosphorus has yielded information regarding nucleotide metabolism in tumour cells. (2) **Therapy.**—Radioactive phosphorus has been used to treat chronic leukæmia and *polycythæmia vera.* There is also a possibility of substituting radioactive cobalt for radium.

Radioactive iodine has been used in thyrotoxicosis and thyroid cancer. Radioactive isotopes may have some carcinogenic action and are liable to exercise a deleterious effect on the reproductive organs if administered before the climacteric.

ALKALIS[1] AND GASTRIC ANTACIDS

THESE drugs when taken by mouth in sufficient dosage neutralise peptic acid. They are used in the treatment of peptic ulcer to reduce pain and promote healing by correcting the state of hyperchlorhydria. Recent evidence suggests that their action is transient owing to the rapid emptying rate of the stomach. There is also evidence that following the neutralisation of gastric hydrochloric acid there is subsequently an increased rate of secretion of the latter, particularly if a rapidly acting antacid like sodium bicarbonate is given. Antacids can be divided into: (*a*) *Systemic antacids* which, in addition to their neutralising action on gastric secretion, increase the bicarbonate of the blood or alkali reserve because of their solubility and ready absorption. They thus have an alkalising effect on all secretions and are capable of causing alkalosis. The latter can result from excessive administration of a systemic antacid or from loss of acid, *e.g.* hydrochloric acid after vomiting, or carbonic acid from overbreathing. Increase in plasma bicarbonate may be corrected by a rise in the blood carbonic acid (corrected alkalosis), but if this does not occur (uncorrected alkalosis) symptoms such as nausea, vomiting, anorexia, abdominal pain and tetany may occur, followed in severe cases by renal failure, coma, and even death. The kidneys endeavour to correct the alkalosis by excreting an alkali urine. The treatment of alkalosis and tetany is discussed on p. 11. Systematic antacids, include sodium bicarbonate and potassium bicarbonate, which increase the alkali reserve directly after absorption, and the acetates and citrates of sodium and potassium, which after absorption are first metabolised to bicarbonates. They are discussed more fully on p. 23. (*b*) *Non-systemic antacids.*—These are generally insoluble compounds and are not absorbed so that they are much less liable to cause alkalosis. Antacids act either by chemical reaction with peptic acid or by binding the latter by physical adsorption. Some compounds such as magnesium trisilicate and aluminium hydroxide combine both effects.

(1) Normally the hydrochloric acid of the gastric juice reacts with the sodium bicarbonate of the intestinal contents to form sodium chloride, carbon dioxide and water. The absorption of these substances and the subsequent excretion of carbon dioxide by the lungs does not affect the acid-base equilibrium of the tissues.

(2) When a systemic antacid like sodium bicarbonate is ingested, it interacts in the stomach with the hydrochloric acid to form sodium chloride, water and carbon dioxide. Eructation of the latter, together with other gases causing flatulent distension, accounts for some of the relief experienced after taking sodium bicarbonate, but its use is not without danger in cases of peptic ulcer on the verge of perforation owing to the initial gastric distension produced by the carbon dioxide. Any ingested sodium bicarbonate not neutralised in the stomach passes into the small intestine where it is absorbed. This results in an increase in the alkali reserve and the other effects discussed above. Such compounds as sodium citrate or acetate, in addition to their

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[1] **The term alkali in the pharmacological sense is not restricted to the chemical definition.**

systemic action, also exercise a buffering action on peptic acid because they are salts of strong bases and weak acids.

(3) When a non-systemic antacid is ingested, such as magnesium oxide, acid is neutralised in the stomach and magnesium chloride formed. The latter passes into the small intestine and reacts with sodium bicarbonate to form magnesium carbonate, sodium chloride, water and carbon dioxide. The magnesium carbonate is unabsorbed, and as some of it is in solution, possibly as bicarbonate and lactate,[1] it may produce a laxative effect. The other products of the reaction are absorbed as in (1) and cause no change on the alkali reserve. When calcium carbonate is given, carbon dioxide and calcium chloride are formed in the stomach. Calcium chloride passes into the small intestine and reacts with sodium bicarbonate to form sodium chloride and calcium carbonate. The latter is insoluble and has a desiccant constipating action. Again there is no change in the alkali reserve. Adsorbent antacids, *e.g.* aluminium hydroxide, act mainly by virtue of their colloidal properties; the acid which is bound in the stomach is liberated in the small intestine and reacts with the sodium bicarbonate as in (1), again producing no change in the alkali reserve.

The following antacid prescription is the type of balanced antacid powder employed in hyperchlorhydric dyspepsia and peptic ulcer:

℞ Sodii Bicarb.
Mag. Carb.
Calcii Carb.
Bism. Carb. .. .. ana gr. xv
ft. pulv. pro dos.

The object of such a powder, given after each feed, is to effect rapid neutralisation of hydrochloric acid by the sodium bicarbonate, this to be followed by the subsequent action of a residuum of the magnesium salt on the increased gastric secretion which follows the initial rapid fall in gastric acid (see above). Bismuth carbonate is not an antacid, but, being an insoluble, fine powder, is added in the hope of spreading a protective film of powder over the ulcer. This conception is probably fallacious. It may be necessary to vary the proportions of calcium or magnesium salts for individual cases according to the effect on bowel action. The transient neutralising action of antacid drugs may be prolonged by the use of preparations of the belladonna group and of olive oil (*q.v.*), which diminish gastric peristalsis and so reduce gastric emptying rate as well as the secretion of hydrochloric acid. An effective method is to introduce 5 pints of milk over the 24 hours by continuous intragastric drip through a Ryles tube passed intranasally.

Bismuthi Carbonas, 10–30 gr.

Bismuthi Oxychloridum, 10–30 gr. (by mouth).

For intramuscular injection in the treatment of syphilis, the official **Injectio Bismuthi Oxychloridi** (*Bisoxyl**), 15–30 min., is employed (*q.v.*)

Borax, 5–15 gr.

Borax in aqueous solution is mildly alkaline antiseptic, antipruritic and detergent.

Glycerinum Boracis, Off. This is used for cleansing the mouth and tongue especially in thrush and aphthous conditions.

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[1] Formed by interaction with lactic acid normally present in the upper portion of the duodenum.

Calcii Carbonas, 10–60 gr. (*Creta*, Chalk).

Taken by itself in small doses, chalk is a useful antacid; in large doses it has a desiccant effect on the contents of the intestine, and is used, often with tannin-containing drugs, in the treatment of diarrhœa.

℞	Calcii Carb.	ʒi
	Tr. Catechu	♏xxx
	Syr. Zingiberis	♏xx
	Tr. Chlor. et Morph.	♏x
	Aq. Menth. Pip.	ad ℥ſs
	ft. mist. pro dos.	

Pulvis Cretæ Aromaticus, Off. 10–60 gr.

Pulvis Cretæ Aromaticus cum Opio, Off. 10–60 gr.

Magnesii Carbonas Levis, 10–60 gr.

Magnesii Carbonas Ponderosus, 10–60 gr.

Magnesii Oxidum Ponderosum, 10–60 gr.

Mistura Magnesii Hydroxidi, Off. 1–4 fl. dr. (Cream of Magnesia, *Milk of Magnesia,** sim.).

The above compounds of magnesium, used in hyperchlorhydria, are converted into magnesium chloride in an acid stomach, and this salt, being indiffusible, acts as an aperient. It is of interest, however, that achlorhydric patients, also, experience an aperient action from these compounds and it may be that soluble salts of magnesium, such as magnesium lactate, are produced in the intestine in such cases.

Mixture of Magnesium Hydroxide is added to infants' milk feeds as a mild alkaline laxative. It is also an efficient dentifrice, for which purpose it can be made more pleasant by the addition of a trace of saccharin and of oil of peppermint. It is a suitable antidote in cases of poisoning with the corrosive mineral acids.

Magnesii Trisilicas, 5–30 gr. (*Magsorbent**).

Magnesium trisilicate is an insoluble powder which is administered as an efficient non-systemic antacid and adsorbent in gastric hyperacidity and peptic ulcer. The magnesium salt of mesotrisilicic acid is used. It adheres to the surface of the ulcer and reacts with HCl to form magnesium chloride and hydrated silicon dioxide. The magnesium chloride is converted in the small intestine into magnesium carbonate and excreted in the fæces, whilst the silicon dioxide acts as an adsorbent. Larger doses than the above are sometimes employed, up to ½ oz., but may cause diarrhœa.

Potassii Bicarbonas, 15–60 gr.

Potassium bicarbonate is more diuretic than the corresponding sodium salt on account of the lower renal threshold of the potassium ion. It is administered as an expectorant, and as an alkaline diuretic in acute cystitis and pyelitis, to relieve pain resulting from highly acid urine, to inhibit *Bacterium coli*, and sometimes in gonorrhœa. The alkali bicarbonates tend to prevent deposition of urates in the urinary passages.

Sodii Bicarbonas, 15–60 gr.

The action of sodium bicarbonate as an antacid has already been discussed. The salt is given in large dosage by mouth to maintain the alkali reserve in acidotic conditions such as diabetic and uræmic coma and cyclical vomiting, and to render the secretions alkaline, especially the urine in scarlet fever, acute nephritis, and in patients on sulphonamide therapy (*q.v.*). *Bacterium coli* infection of the urinary tract is treated by sodium bicarbonate, often combined with sulphonamide therapy. Jaundice and gall-bladder infections are also treated with sodium bicarbonate. Small doses of the salt by mouth help to dissolve mucus in the stomach and so facilitate adequate secretion, *e.g.* in chronic gastritis. This may account for the popularity of alkaline "bitters." Sodium bicarbonate as a 2% solution is recommended for mustard-gas burns of the eye. An alkaline bath, containing about 1 in 150 of sodium bicarbonate, is useful in skin diseases associated with pruritus.

Normal saline containing 3%–5% of sodium bicarbonate may be given intravenously in acidotic coma and eclampsia, but the solution should be freshly prepared, as, on standing, solutions of sodium bicarbonate lose carbon dioxide and the sodium carbonate left behind is caustic to the tissues. Solutions 1%–2% in strength are used as eye lotions and for outward application to relieve mild pruritus; for the latter purpose, however, borax solution is more effective. Half a teaspoonful of sodium bicarbonate sipped slowly in a tumblerful of hot water relieves the paroxysms of coughing associated with chronic bronchitis.

Pulvis Boracis Compositus, B.P.C.

Contains borax, sodium bicarbonate and sodium chloride. A level teaspoonful is added to half a pint of hot water as a sedative and mucus-solvent, nasal douche in chronic catarrh.

Tabellæ Sodii Bicarbonatis Compositæ, B.P.C. (Soda-mint tablets).

These contain sodium bicarbonate flavoured with peppermint and saccharin, and are used as antacid stomachic tablets.

Sodium Alkyl Sulphate.

This compound, recently introduced in America as an antacid, is a combination of sodium palmityl sulphate, sodium oleyl sulphate, sodium stearyl sulphate and sodium lauryl sulphate. The dose is 0·2 gm., 2-hourly.

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Indirect Alkalis

The indirect (or remote) alkalis are the acetates, citrates and lactates of sodium and potassium. They exert a "buffering" effect in an acid stomach, but of more importance is that after metabolism they increase the alkali reserve and have an alkalising action on all secretions. Their actions are fully discussed under other headings.

THE MINERAL ACIDS

Acidum Hydrochloricum Dilutum, 5–60 min. Off.

The gastric juice contains hydrochloric acid which may reach a concentration of 0·5% calculated as HCl, and the average volume secreted is about two and a half pints (1·5 litres) in 24 hours. This acid secretion exercises certain important physiological functions. It activates pepsin, the proteolytic ferment of the stomach, diminishes the activity of ingested bacteria and commences the hydrolysis of disaccharides such as sucrose and lactose. In common with other acidic substances, hydrochloric acid taken by mouth excites the Pavlov reflex. On account of the foregoing, dilute hydrochloric acid is administered to promote digestion in dyspepsia due to hypochlorhydria and achlorhydria associated with some types of chronic gastritis and with pernicious anæmia. Achlorhydric diarrhœa and acne rosacea are treated similarly. In these severe cases, one drachm of the dilute acid with each meal is the usual dosage, and this should be taken well diluted with water, and preferably through a straw. In atonic dyspepsia an acid, bitter mixture such as the following is widely used:

℞	Acid Hydrochlor. Dil.	♏xv
	Tinct. Nuc. Vom.	♏v
	Syr. Auruntii	♏xv
	Spt. Chlorof.	♏v
	Inf. Gent. Co.	ad ℥ſs
	ft. mist.	pro dos.

The dilute acid is given over long periods to asthmatical children, who frequently are deficient in peptic acid, to promote complete digestion of proteins and so prevent absorption of protein antigens often responsible for asthmatic attacks. Since dental caries may arise from prolonged oral administration of mineral acids, the dose is best taken through a straw, as recommended above.

Acidum Hydrobromicum Dilutum, 15–60 min. Off.

This acid differs slightly from the other mineral acids on account of the action of the very small content of bromide ion (v. bromides).

Acidum Nitricum Dilutum, 5–20 min. Off.

Dilute nitric acid has the general properties of the inorganic acids. The concentrated acid is occasionally used to destroy warts, etc.; it leaves a yellow eschar.

Acidum Nitrohydrochloricum Dilutum, 5–20 min.

This has been supposed to be more active than the other dilute mineral acids on account of the traces of reaction products which it contains.

Acidum Phosphoricum Dilutum, 5–60 min. Off.

In the treatment of deficiency of natural acid, dilute phosphoric acid is sometimes used, as it is possible to exhibit it as a more pleasant acidulous draught than can be prepared with dilute hydrochloric acid. It is sometimes used instead of sodium acid phosphate to acidify the urine by depleting the intestine of alkali.

Acidum Sulphuricum Dilutum, 5–60 min. Off.

Dilute sulphuric acid precipitates protein, and in the stomach it delays relaxation of the pyloric sphincter; thus passage of food from the stomach is retarded. On this account it has been used in the treatment of obstinate diarrhœa and the milder forms of dysentery. The following is a suitable mixture:

℞	Acid. Sulph. Dil.	♏xxx
	Tinct. Opii	♏x
	Syr. Zingib.	ʒi
	Aq. Cinnam.	ad ℥i
	ft. mist.	pro dos.

The dilute acid, usually disguised as completely as possible by syrup and fruit essence, is given to lead workers to render insoluble any lead which may have been ingested, and so act prophylactically against plumbism.

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To find an account of the various salts of the foregoing acids the index should be consulted.

THE ORGANIC ACIDS AND THEIR SALTS

Acidum Aceticum Glaciale.

Glacial acetic acid is applied externally, with a glass rod, as an escharotic.

Acidum Aceticum Dilutum, 30–60 min.

Given by mouth, dilute acetic acid is a sialagogue and reflexly provokes improved gastric secretion. It mildly irritates the gastric mucosa, and is used as a reflex expectorant, combined with other expectorant drugs (*vide* Scilla).

Potasii Acetas, 15–60 gr. (*q.v.*).

Liquor Ammonii Acetatis Dilutus, ½–1 fl. oz. Off.

Liquor Ammonii Acetatis Fortis, 15–60 min. Off.

These preparations are used as saline diaphoretics and diuretics (*q.v.*). Ammonium acetate is excreted as urea, carbon dioxide and water.

Acidum Benzoicum, 5–15 gr.

For an account of the expectorant action of the benzoates, see the chapter on Expectorants. Benzoic acid is used as an antiseptic, especially in fungous infections of the skin. It may be used as a lotion (50% in 40% alcohol) or as an ointment (5%).

Unguentum Acidi Benzoici Compositum, B.P.C. (Whitfield's Ointment).

This contains benzoic 5% and salicylic acids 3%, and is used in diseases of the scalp such as ringworm, and in dermatophytoses generally. When there is much hyperkeratosis these proportions may be doubled.

Sodium Benzoate.

This salt is given by mouth in doses of 6 gm., or intravenously 20 mil. of 8·85% solution in the hippuric acid synthesis test of liver function. In liver disease there is a reduced ability on the part of the liver to synthesise hippuric acid from the benzoate, so that less is excreted from the liver.

Ammonii Benzoas, 5–15 gr.

Is given orally to increase urinary acidity; it is excreted as hippuric acid and urea.

Calcium o-iodoxybenzoate (*Calsiod**). Dose: 0·5 to 1 gm. 3 times daily, oral.

Ammonium Ortho-iodoxybenzoate (*Arthrytin**). Dose: 0·75 to 1 gm. intravenously; double this dose orally.

These drugs, used in rheumatoid arthritis, are of doubtful value and may produce gastric upset and febrile reactions.

Methyl-p-hydroxybenzoate (*Phytodermine**).

Used in combination with salicylates as a fungicidal dusting powder.

Recent therapeutic trials in America suggest that the calcium double salt of benzoic acid and succinic acid benzyl ester is more efficacious than salicylates in the treatment of acute rheumatism. As succinic acid acts as a catalyst in tissue oxidations, the therapeutic effect of the above compound may depend upon its correcting deranged tissue oxidation in rheumatic fever.

Benzoinum.

Benzoin is an aromatic gum-resin containing free benzoic and cinnammic acids, and certain of their esters.

Tinctura Benzoini Composita, ½–1 fl. dr. Off. (Friar's Balsam).

The tincture is seldom given internally. It is used principally as an inhalant with hot water, in laryngitis, chronic bronchitis and sinusitis, in the proportion of one teaspoonful to a pint of very hot water.

Acidum Citricum, 5–30 gr.

Citric acid enters largely into the composition of lemon-flavoured, acidulated drinks, for use in fevers, and as cooling beverages generally. The acid is converted into citrate in the intestine. Large doses may produce acidosis, since the citrate formed is only partly absorbed and metabolised, the remainder being excreted by the bowel with ultimate drainage of alkali from the tissues. "Solution G," containing citric acid (monohydrate) 32·25 gm., magnesium hydroxide (anhydrous) 3·84 gm., sodium carbonate (anhydrous) 4·37 gm., and water up to 1 litre, has been recently employed to dissolve away urinary calculi composed of calcium phosphate, calcium carbonate or magnesium ammonium phosphate. The urinary tract is irrigated with the solution, which must be kept in constant contact with the calculus. "Solution M" is a modification of the above in which the amount of sodium carbonate is increased to 8·84 gm.

Potassii Citras, 15–60 gr.

Potassium citrate is partly diffused from the intestine, and is metabolised to bicarbonate and excreted as such, thus acting as a diuretic and making the urine alkaline. It is mainly used in the treatment of *Bacterium coli*, cystitis and pyelitis. The salt is expectorant, since the bronchial secretion tends to become alkaline, and tenacious mucus is rendered more fluid. In all respects these actions are more marked in the case of potassium acetate, since the latter is completely absorbed from the intestine.

Sodii Citras, 15–60 gr.

Sodium citrate possesses the same properties as potassium citrate, but it is less diuretic owing to the higher renal threshold of the sodium ion. Added to blood, it depresses the ionisation of calcium, so inhibiting thrombin formation and preventing clotting. For this reason it is added to blood withdrawn for transfusion. The addition of sodium citrate to milk helps the formation of smaller, hence more easily digested, curds, again by its action on the calcium content. Sodium citrate is said to accelerate coagulation when administered intravenously or intramuscularly. A 5% solution may be used intravenously or 15 mils of a 30% solution injected into each gluteal muscle for this purpose. It is possible that hypertonic solutions of this character may accelerate clotting by causing a diffusion of coagulating bodies from the connective tissues into the blood. Di-sodium hydrogen citrate does not neutralise gastric juice and has the same systemic uses as sodium citrate.

Injectio Sodii Citratis Anticogulans, Off.

This contains 2·5% of sodium citrate and 0·9% of sodium chloride.

Injectio Sodii Citratis cum Dextrose, Off.

Contains 2·5% of sodium citrate and of dextrose.

Acidum Lacticum, 5–20 min.

Concentrated lactic acid is employed as a caustic to destroy tuberculous ulceration of the larynx and pharynx. Solutions (10%) are employed internally, instead of medication with cultures of *Bacillus acidophilus*, etc., with the purpose of changing the intestinal flora from a pathogenic to a benign character.

A 5% solution may be used as a vaginal douche for antiseptic and contraceptive purposes.

Various types of chronic arthritis and traumatised joints have been successfully treated by the injection into the affected joint of 0·5% procaine hydrochloride solution acidified to pH 5 with lactic acid, this solution being termed P.L.A. The rationale of the treatment is that an acid medium in the synovial fluid evokes a physiological response stimulating leucocytosis and repair: the liquid itself acts also as a lubricant. It is a useful measure when other treatment has failed, and should not be used when the synovial fluid is already acid. An effective alternative solution contains 0·5% procaine hydrochloride adjusted to pH 7·6 with sodium phosphate.

Sodii Lactas, 5–10 gr.

Sodium lactate acts as a remote alkali, and for this reason enters into the composition of Hartmann's fluid (*q.v.*). In solution one-sixth molar in concentration, the salt is given intravenously in severe acidosis, *e.g.* diabetic coma.

Injectio Sodii Lactatis Composita, Off. (Hartmann's fluid).

This contains 0·3% sodium lactate with the chlorides of sodium, potassium and calcium. It is isotonic with blood.

Lac Coactum, B.P.C.

Curdled (or soured) milk is prepared by adding cultures of *B. acidophilus* or *B. bulgaricus* to sterile milk. The product is designed to inhibit the proliferation of putrefactive micro-organisms in the intestine.

Lactic acid milk (1 drachm to the pint) and hydrochloric acid milk (40 minims to the pint) are prepared by the gradual addition of the acid. Both products are used in gastro-enteritis associated with deficiency of peptic acid, and in infant feeding, where similar deficiency may result in protein dyspepsia, and be a factor in the causation of eczema and asthma.

Acidum Salicylicum, 5–10 gr.

Salicylic acid is a tissue solvent and is rarely given by mouth; the specific action of the salicylate ion is discussed under sodium salicylate. Externally, salicylic acid is applied in ointment form to soften hard skin and, dissolved (10%) in collodion, to remove corns and warts. It is a frequent component of ointments intended to remove the horn cells of the epidermis and so promote the penetration of other medicaments. Applied locally it is antiseptic, antipruritic and fungicidal. (See Lassar's Paste, p. 18.)

Unguentum Acidi Salicylici, Off.

Bismuthi Salicylas (*q.v.*).

Methylis Salicylas, 5–15 min.

Methyl salicylate occurs in certain natural essential oils such as that of gaultheria (Wintergreen). The synthetic product is, however, much more widely used. It is applied to intact skin for the relief of fibrositis, inflamed joints, etc. Locally there is a mild rubifacient action, and owing to complete and rapid absorption through the skin the characteristic systemic effects of the salicylates may develop.

Linimentum Methylis Salicylatis, B.P.C.

The rubefacient and analgesic effects of methyl salicylate are reinforced in this liniment by the addition of camphor and menthol.

Ungentum Methylis Salicylatis, B.P.C.

Sodii Salicylas, 10–30 gr.

Sodium salicylate is rapidly absorbed and it exerts a diaphoretic effect, partly by salt action and partly by depressing the central heat-regulating mechanism. It thus possesses antipyretic properties in all febrile conditions, but more specifically in acute rheumatism, abating both pyrexia and arthritis. A recent suggestion of the mode of action of sodium salicylate is that it inhibits hyaluronidase, an enzyme produced by many organisms, including the hæmolytic streptococcus. Hyaluronidase is the "diffusion factor" which helps in the spread of exudates and micro-organisms in the tissues. This it does by neutralising hyaluronic acid, the principal substrate of mesenchymal tissues such as the synovia and ligaments of joints. Thus the inhibition of hyaluronidase by salicylates would help to limit the spread of infection. In the early stages of rheumatic fever it should be given in large doses with sodium bicarbonate. The latter obviates the liberation of free salicylic acid in the stomach and during excretion in the urine, so preventing irritation. Sodium salicylate is partly excreted with the bile, and exerts some cholagogue effect, but the major part appears in the urine as sodium salicylurate. In view of the increased excretion of urates when the drug is administered, it is sometimes used in the treatment of chronic gout, although it is not so effective as cinchophen or aspirin. For acute rheumatism:

℞ Sodii Salicyl. .. .. gr. xx
Sodii bicarb. .. .. gr. xxx
Aq. Menth. Pip. .. .. ad ℥i
ft. mist. pro dos. every two hours.

It is suggested that a more effective way of maintaining a therapeutic concentration of sodium salicylate in the blood is to administer the drug by intravenous drip, 10 gm. in 1 litre normal saline being given 4-hourly for 4 days, but such therapy is unnecessary and may be dangerous.

There is little evidence of the value of sodium salicylate therapy in fibrositis and chronic rheumatism of the joints.

Intolerance to salicylates is evidenced by tinnitus, deafness, visual disturbances, sweating, headache, vomiting, rash, etc. Some cases exhibit marked dyspnœa, albuminuria and collapse.

Acidum Tartaricum, 5–30 gr.

Tartaric acid has properties similar to those of citric acid (*q.v.*). The tartrates of sodium and potassium, however, are very poorly diffused from the intestine and, in sufficient dosage, they exert an aperient action. Frequent doses of tartaric acid by mouth promote loss of alkali from the intestine and cause mild acidosis. This may account for the lassitude sometimes produced by "fruit" drinks containing tartaric acid when imbibed freely during sultry weather.

Pulvis Effervescens Compositus (Seidlitz Powder), Off.

Seidlitz powder is a popular, effervescent saline aperient.

Sodii et Potassii Tartras (Rochelle Salt), 2–4 dr.

Rochelle salt is a useful saline aperient, especially for children, as it is not so unpleasantly saline in taste as the sulphates of sodium and magnesium.

THE GENERAL ACTION OF SALTS

A SALT is the product of interaction between an acid and a base. Like all substances in the crystalloid state in solution, salts exert osmotic pressure on semi-permeable membranes, and since, in contradistinction to non-saline crystalloids, urea, sugar, etc., they are ionised, the osmotic pressure which they exert is governed by four factors:

1. Molecular weight.
2. The strength of the solution.
3. The number of ions yielded by the salt.
4. The degree of ionic dissociation.

Solutions which exert the same osmotic pressure as the body fluids are said to be isotonic therewith. A blood-cell placed in a solution approximately isotonic with the plasma will exhibit no alteration in size. A strongly hypertonic solution will shrink the cells, whilst a solution of very low tonicity will cause the membrane to swell up and rupture. Solutions prepared for parenteral use, unless of very small bulk, are made isotonic with the plasma, and eye lotions, nasal washes, etc., are liable to cause acute discomfort or pain, unless a similar precaution is taken. The following strengths of solution of the substances named are approximately isotonic with the plasma:

Borax	3%
Calcium Chloride	1·2%
Dextrose (glucose)	5%
Sodium Bicarbonate	1·35%
Sodium Chloride	0·9%
Sodium Citrate	3·8%
Sodium Phosphate ($Na_2HPO_4.12H_2O$)	4·5%
Sodium Sulphate ($Na_2SO_4.10H_2O$)	4·4%

In the body, the cell cytoplasm acts as a semi-permeable membrane and it exercises the almost totally unexplained action of selective absorption. Thus some saline ions, and certain other crystalloids, will exert the purely physical phenomenon of osmotic pressure in contact with cells, others will be fully absorbed; some will irritate or poison the cytoplasm. We must also visualise in the tissues an interplay of ions modifying each other's action on the protoplasm; the magnesium ion is a general protoplasmic poison, but it is antagonised by calcium; the ions of calcium and potassium are mutually antagonistic. In health there exists a fairly constant ionic balance, and it is primarily the function of the kidneys to maintain this balance and also the correct proportion of the blood crystalloids.

The body water is divided between the intracellular and extracellular fluids, the latter including the plasma and tissue fluids. Potassium and phosphates and, to a less extent, magnesium, calcium and sulphate are the important ions of the intracellular fluids. The extracellular fluids, on the other hand, contain mainly sodium and chloride and, to a less extent, bicarbonate, the plasma having a similar composition to the tissue fluids except that it contains protein. The plasma and tissue fluids communicate with each other through the capillary loops, the hydrostatic pressure of the blood causing fluid to leave the blood through the proximal end of the loop, and the osmotic action of the plasma proteins resulting in a return of fluid to the blood through the distal end where the hydrostatic pressure is low. Sodium and chloride are also important constituents of the alimentary secretions, urine and sweat. The main physiological functions of the extracellular ions is to maintain the isotonicity of the intracellular fluids as well as to regulate the acid-base equilibrium of the extracellular fluids, which are maintained slightly alkaline. Most alimentary secretions are isotonic with the tissue fluids, although their reactions differ widely. The acid gastric secretion depends upon the much greater secretion of chloride as compared with sodium, whilst the alkalinity of the pancreatic juice is determined by the greater secretion of sodium. The tears, formerly thought to be hypertonic, are now known to be isotonic with the plasma. The kidneys play an important part in maintaining the isotonicity of the extracellular fluids by selective absorption through the tubules of the components of glomerular filtration, particularly sodium, chloride and water. When renal impairment occurs, there is a relative inability to excrete and concentrate sodium chloride, with the result that there is salt retention with a tendency to œdema[1] of the tissues, particularly if saline is administered. This danger is more marked in babies who excrete salt much less readily. The kidneys also assist in maintaining the normal reaction (pH 7·4) of the blood by eliminating either acid phosphate (NaH_2PO_4) or alkaline phosphate (Na_2HPO_4), according to requirement. Plasma phosphate is the mildly alkaline di-sodium salt Na_2HPO_4. When loss of alkali occurs, the cytoplasm of the tubular epithelium withdraws one of the sodium atoms, replacing it with hydrogen, so forming the acid phosphate NaH_2PO_4 which is excreted. The sodium is combined with hydroxyl and with the carbon dioxide present in solution, and returned from the tubules to the tissues as sodium bicarbonate.

Other important regulating mechanisms in maintaining isotonicity of the body fluids are: (1) the suprarenal glands, important in restricting excessive excretion of salt by the kidneys. This mechanism fails in Addison's disease; (2) there is a hypothalamic-pituitary mechanism regulating water metabolism, and deficiency of the posterior pituitary secretion results in the failure on the part of the kidney tubules to reabsorb water so that polyuria occurs, a condition met typically in *diabetes insipidus*. The secretion of the antidiuretic hormone is determined by the osmotic pressure of the plasma, changes in this pressure influencing "osmoreceptors" which regulate the production of the antidiuretic hormone. The effects of salt and water depletion are considered in the section on sodium chloride. Other results of disturbances in ionic balance are considered in the sections on calcium, potassium and alkalosis.

The sodium ion is practically non-toxic, and it is usual to administer the sodium or potassium salts when the action of the acidic radicle is the one primarily desired. Potassium is innocuous in small doses, and, indeed, may be beneficial to civilised man who is supposed to suffer from some degree of potassium deprivation. Potassium salts are more diuretic than the corresponding salts of sodium, since potassium has a lower renal threshold. In large or long-continued dosage potassium is depressant to the heart, which may be arrested in diastole, and to the central nervous system.

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[1] Nevertheless, salt retention is not the primary cause of renal œdema; reduced colloidol osmotic pressure, due to loss of protein in the urine, and increased capillary permeability in the tissues, are much more important factors.

Taken by the mouth, salts are diversified in their action, since any or all of the following factors may have to be taken into consideration:

(*a*) Local action on the alimentary tract.
(*b*) Reaction with the gastric acid.
(*c*) Reaction with the intestinal alkali.
(*d*) Solubility and diffusibility of the products of (*b*) and (*c*).
(*e*) Specific action, after absorption.
(*f*) End-products if metabolised.

Since specific actions (*e.g.*, that of the bromides) are considered elsewhere, we need here concern ourselves only with the other considerations. The first local action is in the mouth, where soluble salts possessing a "saline" taste give rise to the Pavlov reflex. This is well exemplified by sodium chloride, and it will be convenient to consider first the fate of a substance such as sodium chloride which is absorbed unchanged from the intestine. In the alimentary tract the salt solution tends to be modified by concentration or dilution until it is isotonic. Diffusion of the salt in solution occurs, and unless the subject is suffering from dehydration a temporary hydræmia is produced which will tend to give rise to diuresis and diaphoresis. The salt is excreted unchanged by the kidneys. Another example is potassium nitrate. Potassium has a low renal threshold and the nitrate ion is foreign to the tissues; marked diuresis therefore occurs. If we now consider sodium acetate, this salt may be partly changed into chloride in the stomach, but for all practical purposes it can be regarded as being absorbed unchanged from the intestine, and in large doses it acts as a saline diuretic, expectorant and diaphoretic. The sweat glands are called upon to function briskly in order to assist in eliminating the foreign salt. The acetate radicle, however, is metabolised, forming sodium bicarbonate, which is excreted by the kidneys and renders the urine alkaline. The citrates, lactates and tartrates of sodium and potassium behave in a similar fashion, but vary in alkalising power according to their diffusibility from the intestine. The tartrate radicle being only very slightly absorbed is aperient, and the following table shows the variation in action between the three commonest remote alkalis:

	Degree of Absorption.	Action.
Acetate (of Sodium or Potassium)	Complete	Diuretic
Citrate (of Sodium or Potassium)	40%–50%	Less Diuretic
Tartrate (of Sodium or Potassium)	Slight	Laxative

Salts of ammonium behave somewhat differently from those of the fixed alkalis because the ammonium radicle, itself, undergoes metabolism. In the case of ammonium chloride the ammonium is converted by the liver into urea and excreted as such by the kidneys. The hydrochloric acid, liberated during the process, is neutralised by alkali from the tissues, hence, in compensation for the loss of alkali, acid phosphate is excreted in the urine to maintain the tissue reaction at normality. The administration of a dose of ammonium chloride therefore involves the formation of three crystalloid substances—viz., urea, sodium chloride and sodium acid phosphate, all of which are excreted by the kidneys, increasing the urinary output and rendering it acid. If the dosage of ammonium chloride be large, some of it is excreted unchanged. Acetate and citrate of ammonium undergo a similar transformation as regards urea formation, but the acidic radicles are metabolised to carbon dioxide and water; no change in the reaction of the urine occurs, therefore, because the only substance excreted by the kidneys is the urea produced. An interesting action is observed when calcium chloride is given by mouth; it is partly converted into calcium bicarbonate and carbonate in the intestine, and a proportion of the former, together with unchanged calcium chloride, is absorbed. The chloride ion is absorbed as sodium chloride and excreted as such, and loss of alkali in the intestine is made good by fresh supplies from the tissues. In consequence of this loss of alkali, sodium acid phosphate appears in the urine and calcium chloride has, therefore, a marked acidifying and diuretic effect. The action is not very pronounced when the drug is given in small doses by mouth, but intravenous infusions of calcium chloride produce acidosis very easily, since the calcium circulates principally as proteinate, leaving the chloride ion to combine with, and consequently deplete, the tissue alkali. It is to be observed that the diuretic action is not directly produced by the calcium, for even when injected into the tissues it is largely excreted into the bowel; diuresis results from the formation of sodium chloride and of sodium acid phosphate (NaH_2PO_4), and from the acidotic state which appears to diminish the water-carrying capacity of the tissue colloids. The latter salt, itself, is often given by mouth to render the urine acid, especially in conjunction with hexamine (*q.v.*) in the treatment of urinary infection. The salt is not absorbed, but it reacts with more base in the intestine to form the normal phosphate (Na_2HPO_4); this drains alkali from the tissues with a result similar to that described under calcium chloride. Thus, although sodium acid phosphate is given by mouth and sodium acid phosphate appears in the urine, the latter does not consist of the same individual molecules which comprised the oral dose. It is important that the student should clearly comprehend this if he is to understand the acid-base equilibrium of the tissues adequately.

Sodii Chloridum.

Sodium chloride depletion in the body constitutes the chief indication for therapy with this salt and is a very important condition, often confused in the past with the effects of water depletion, with which it may be associated and from which it must be distinguished. **Water depletion** results from deprivation or from inability to swallow from great physical weakness or pharyngeal or œsophageal obstruction. It causes a rise of the osmotic pressure of the extracellular fluids from lack of water, and this is followed by the passage of water from the cells into the extracellular fluids until the osmotic balance is restored. There is thus a cellular dehydration. Symptoms include thirst, pinched facies, dry tongue, oligouria, weakness and mental impairment. The urine contains chlorides, the blood chlorides are normal or slightly increased, and the blood urea is raised. Death may occur, possibly as the result of the general rise in osmotic pressure. Treatment is to give water either by mouth when it is rapidly absorbed from the intestine, or, in severe cases, parenterally with 5% (isotonic) dextrose. The administration of sodium chloride solutions in pure water depletion is deleterious as it increases the concentration of the extracellular fluids and thus forces more work on the kidneys in the excretion of salt. This may be particularly harmful in infants who excrete and concentrate salt in the urine with much greater difficulty than adults. The effects of water depletion is aggravated by renal impairment, because, owing to the inability to excrete a concentrated urine, larger quantities require to be excreted. Infants, too, suffer more severely from water depletion, because their relatively poor powers of renal concentration necessitate the excretion of larger amounts of urine. **Salt depletion** is due to abnormal loss of alimentary secretions, sweat or urine. Excessive loss of alimentary secretions occurs in: (1) prolonged vomiting when the condition is due mainly to loss of chloride ions with a consequent tendency to alkalosis; (2) marked diarrhœa, in which the loss of sodium ions results in a tendency to acidosis; (3) gastric or intestinal suction therapy, unless accompanied by the administration of parenteral saline. Excessive loss of salt in the urine occurs in Addison's disease. Severe sweating results from febrile states and from raised atmospheric temperatures. Loss of sodium chloride from the extracellular fluids produces a fall in their osmotic concentration and this causes an increased excretion of water by the kidneys until isotonicity is restored. There is a consequent fall in plasma volume with hæmoconcentration, increased blood viscosity, cramp, marked rise in blood urea, fall in blood pressure and symptoms of peripheral circulatory failure. A fall in the plasma sodium chloride occurs, and the salt is absent from the urine except in Addison's disease. The volume of urine is undiminished until peripheral circulatory failure and uræmia appear. Weakness, headache, vertigo, syncope, cramps, mental confusion, anorexia and vomiting may occur, the latter increasing the severity of the condition. Death may result. In contrast to water depletion, there is an absence of thirst as well as of chlorides from the urine, and absorption of ingested water from the alimentary tract is slow as the result of pylorospasm. Symptoms of alkalosis, acidosis or water depletion may be superadded. In treatment it is essential to administer sodium chloride as isotonic saline when symptoms are present and chlorides are absent from the urine. Later, when urinary chlorides have reappeared and in order to avoid the danger of excessive salt administration with salt retention and œdema, it is desirable to employ either half-normal saline with 2½% dextrose or $\frac{1}{5}$ normal saline with 4·3% dextrose, such solutions being isotonic. The use of these low sodium chloride solutions is particularly important in infants, in whom it is safer never to employ normal saline owing to their greater difficulty in eliminating salt. These low sodium chloride solutions are useful in mixed salt and water depletions. In severe cases, the fluids should be administered intravenously by the continuous drip method, and when the condition improves, and the tendency to vomit ceases, the oral route is usually adequate. When patients are unable to drink, fluids can be given through a Ryles tube passed intranasally into the stomach. Rectal, intramuscular or subcutaneous administration may prove useful in the less severe type of case. The amount of salt required varies and is equivalent to 4 to 10 litres of normal saline according to the severity of the case. In a very ill patient it may be necessary to administer the first litre within half an hour. In

Addison's disease during the crises, sodium chloride is given intravenously, as above, together with cortin (*q.v.*). Later it is continued by oral administration in doses of 15 gm. daily. Mention should be made of the occurrence of symptoms of salt depletion in some patients who remain on salt-free diets for long periods. The parenteral administration of isotonic saline with 5% dextrose in various types of shock is commonly practised. Salt depletion is a feature in many of these states. The added dextrose provides a readily utilisable form of energy for the heart and tissues. Some clinicians prefer Hartmann's fluid (*q.v.*) in place of the simple solution of sodium chloride. Gum-saline or plasma is to be preferred in traumatic shock or where there is a fall in the plasma proteins, except when the shock is due to hæmorrhage, when blood transfusion is necessary; the presence of colloid retards the loss of salt and fluid. Solutions of dextrose and sodium chloride are used also as vehicles for the administration of intraspinal anæsthetics. Strongly hypertonic solutions (30%) of sodium chloride are sometimes injected to relieve high intracranial pressure by osmosis through the choroid plexus. In cases of anuria a 15% solution is given intravenously to promote diuresis; it is inferior, however, to isotonic sodium sulphate solution (*q.v.*) for this condition, since sodium sulphate as a foreign salt is more rapidly and completely eliminated. A 20% solution has been employed to sclerose varicose veins, but it is not satisfactory. A 5% solution is used as a rectal injection to expel thread worms. Sodium chloride is added to nasal and eye lotions, etc., to maintain tonicity and is used externally as a 5 to 10% solution (usually with ½ to 1% sodium citrate) in the hypertonic treatment of septic wounds. It is sometimes given by mouth in large doses to irritate the gastric mucosa and produce emesis, also in the treatment of bromism (*q.v.*). A fluid bearing a much closer resemblance to the plasma (without the proteins) is Hartmann's fluid (*q.v.*).

Further reference to salt action will be found in the chapters dealing with Diuretics, Expectorants, Laxatives and Metals.

Injectio Sodii Chloridi et Acaciæ, B.P.C. (Gum-Saline)

Injectio Dextrosi, Off.

Injectio Sodii Chloridi, Off. (Normal Saline).

It contains 0·9% sodium chloride, and is isotonic with the plasma **and with tear secretion.** The latter was formerly thought to be isotonic with a 1·4% solution of sodium chloride.

THE AUTONOMIC NERVOUS SYSTEM

THE autonomic nervous system controls, in the main, smooth muscles and the glands. It comprises two divisions: sympathetic and parasympathetic. The head ganglia of the autonomic are considered to lie in the hypothalamus, but, in contradistinction to the somatic nervous system, the excitor cells of the efferent paths of the autonomic system occur outside the central nervous system. The sympathetic excitor cells usually lie near to the central nervous system, forming the sympathetic chain of ganglia, while those of the parasympathetic are usually remote—that is, near to the organ or tissue they innervate. The parasympathetic comprises the vagus and other innervations which develop from the mid-brain, the medulla and the sacral region of the cord. According to the modern theory, communication between the tissues under autonomic control and the nerve is mediated by chemical stimuli, which appear at the nerve ends. These chemical substances act directly on the tissues and bring about the phenomena which characterise stimulation of one or the other branch of the autonomic system. Sympathetic stimulation is mediated by adrenaline[1]; that of the parasympathetic by acetylcholine. The terms **adrenergic** and **cholinergic** respectively are used to describe the two types of nerve fibres. The function of the sympathetic being to reinforce the central nervous system in crises, a clear conception of the action of adrenaline can be gained by visualising all the physical reactions to the emotions of terror or pugnacity, and reasoning out the physiological significance of the effects produced. In other words, the physical resources are mobilised for fight or flight. To adrenaline, therefore, the term sympathomimetic is applied.

The parasympathetic functions are not difficult to memorise since in tissues where both innervations occur their actions are opposite. Briefly summarised, the effects of the **parasympathetic** stimulation are:

Eye: Miosis and decreased intra-ocular tension.

Glands: The secretion of most glands is augmented.

Bronchi: The muscle tone is increased and bronchospasm may follow overstimulation.

Alimentary Tract: The sphincters are relaxed and muscle tone improved. Vomiting and diarrhœa result from excessive activity.

Uterus: A proportion of the sympathetic nerve supply is cholinergic, these fibres are motor to the organ.

Heart: The vagus is inhibitory, slowing the heart, diminishing the force of its contraction and producing varying grades of heart-block.

Voluntary Muscle: The humoral conveyance of motor impulses to voluntary muscle is by acetylcholine. In the condition of *myasthenia gravis* the muscles are subnormally responsive to acetylcholine, and the disease may be benefited by the use of *Prostigmin** (*q.v.*) or by a sympathomimetic drug, since adrenaline directly stimulates the skeletal muscle fibres.

It should be noted that **afferent** vagal stimulation has been shown experimentally to produce dilatation of the cerebral vessels, and **efferent** sympathetic stimulation, their constriction. Persons in whom one or the other of the autonomic groups patently predominate are sometimes classed as sympathotonic and vagotonic respectively. Sympathomimetic drugs are liable to produce a feeling of intense anxiety with some patients.

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[1] Theories relating to Sympathin I & II are too involved for discussion in a book of this concise character.

Drugs acting on the Sympathetic

Adrenalina (Epinephrine), $\frac{1}{600}$–$\frac{1}{120}$ gr.

Adrenaline is a hormone produced by the medulla of the suprarenal gland. It is believed to be stored at the sympathetic nerve ends in an inert form (possibly noradrenaline) which is activated by the passage of a nerve impulse. It is alcoholic and phenolic in structure and its solutions are unstable; by mouth it is rapidly destroyed by the digestive juices. When injected into a vein its effects are comparable to a powerful but somewhat transient stimulation of the sympathetic nervous system. It has, however, no sudorific action, since the sweat glands are innervated by cholinergic sympathetic fibres. A rapid but very transient rise of blood-pressure occurs, due to constriction of the splanchnic and other vessels, especially the arteries and arterioles, and adrenaline is sometimes used to combat shock, but its action is too transient to be of much value. It may be given, also, by intravenous or intracardiac injection, against collapse during operations, etc. Adrenaline accelerates and augments the heart and increases its conductivity, hence the drug is injected intravenously or intracardially in heart-block with Stokes-Adams attacks. With the rise in blood-pressure an increased volume of blood flows through the coronary arteries, which are dilated, since, in contra-distinction to the usual rule, these vessels are dilated by the sympathetic and constricted by vagal action. The cerebral blood supply also is increased. The bronchial muscle is inhibited by the sympathetic, and adrenaline may be injected subcutaneously, or preferably intramuscularly, to dilate the bronchi and abolish the spasm of asthma. In status asthmaticus, the drug should be injected hypodermically at the rate of 1 minim every half to one minute, with the syringe left *in situ*, until the attack is relieved; as much as 60 minims or more may be required in severe cases. Slow liberation of the drug with prolongation of its action can be obtained: (1) by giving the drug in oily solution intramuscularly, 1 ml. being equivalent to 2 ml. of Liq. Adrenalin. Hydrochlor.; (2) by administering the drug as the mucate (*Hyperduric Adrenaline**). In asthma it is sometimes used in combination with pituitrin (*Pitrenalin**). A 1 : 100 solution sprayed down the throat, or vaporised and inhaled, is sometimes employed as an alternative to parenteral administration for the relief of bronchial asthma. Allergic skin disturbances, such as urticaria, may be abbreviated by the vasoconstrictor action of the drug. When injected, adrenaline mobilises glycogen reserves and may give rise to glycosuria; it therefore affords a useful and rapid means of treating insulin shock. Its action on the gut is to dilate the lumen and constrict the sphincters; it diminishes movements of the tract and abolishes hunger-pain. On skeletal muscle the hormone has a transient stimulating effect apparently on the cell cytoplasm, accelerating recovery from fatigue. Adrenaline hydrochloride (1 : 10,000 to 1 : 30,000) is combined with procaine hydrochloride, etc., to localise and so intensify the anæsthetic action when used subcutaneously; stronger solutions are inadvisable owing to the risk of gangrene from prolonged ischæmia. When large doses of adrenaline solution are required, they should be given intramuscularly. Adrenaline is often prescribed in oily or aqueous solution for local application in rhinitis, hay fever, etc. There is, however, a growing opinion that vasoconstrictor drugs should be used with caution in these states, being employed at not too frequent intervals and for only a few days at a time. They afford only temporary relief and the vascular relaxation gradually worsens. The topical application of adrenaline (1 : 10,000) to the eye blanches the conjunctiva. A solution of similar strength is employed on gauze to pack the nose as a pre-operative precaution against hæmorrhage from nasal operations, and as a local hæmostatic, generally. Like other sympathomimetic drugs, the use of adrenaline is liable to produce a mental reaction characterised by restlessness and anxiety. If the drug is injected the pupils are dilated, and in parturient women the uterus is inhibited.

Injectio Adrenalinæ, Off., 2–8 min.

A sterilised and relatively stable solution.

Liquor Adrenalinæ Hydrochloridi, Off.

A stabilised solution containing 1 : 1,000 of adrenaline for local use. Adrenaline tartrate and borate are alternative preparations.

Nebula Adrenalinæ et Ephedrinæ, B.P.C.

A nasal spray solution containing 1 : 8,000 of adrenaline with ephedrine 1 : 45 in an aqueous medium.

Nebula Adrenalinæ et Ephedrinæ Oleosa, B.P.C.

Adrenaline 1 : 10,000, ephedrine 1 : 50, menthol, eucalyptol in oily base.

Nebula Adrenalinæ et Cocainæ, B.P.C.

Adrenaline 1 : 5,000, cocaine 1 : 100, chlorbutol, sodium chloride in aqueous medium.

Extractum Suprarenalini Corticis, B.P.C. (Cortin, *Eucortone**), 1½–2½ fl. dr.

The suprarenal cortex is essential for normal metabolism; destructive changes in it (Addison's disease) are accompanied by metabolic derangements. The blood-sugar level falls and glycogen stores are depleted, causing asthenia, and there is an enormous increase of sodium (and chloride) excretion with a concomitant rise of the potassium content of the tissues. The blood-volume and blood-pressure are low. These changes can be reversed by the parenteral administration of cortin, and the dose of the latter can be reduced by the concurrent oral administration of sodium chloride, about half an ounce daily. During the crises of Addison's disease glucose-saline may be given intravenously as well. Cortin is also of value in the treatment of shock and toxæmia due to burns, but is apparently of little value against traumatic shock in general.

Desoxycorticosterone Acetate (*D.O.C.A.**), $\frac{1}{30}$–$\frac{1}{6}$ gr. (2–15 mg.).

The active principle of cortin appears to be mainly, but not entirely, corticosterone. Synthetically prepared desoxycorticosterone is about ten times more potent and may be administered by intramuscular injection in oily solution, or by the implantation of pellets (50–150 mg.) into the rectus sheath of the abdominal wall. A single implantation will often serve to maintain a case of Addison's disease for months. The actions and uses of this steroid are similar to those of cortin, but it is not a complete substitute for the extract and some cases do better on the latter. It is of much less value in the crises of Addison's disease. Toxic effects such as œdema, hypertension and hypoglycæmia may develop. During treatment with this synthetic product there must be an adequate **potassium** intake as the level in the tissues falls.

Amphetamina (*Benzedrine**).

This sympathomimetic base was originally introduced as an inhalant for the relief of nasal catarrh and hay fever by causing vasoconstriction. When employed for this purpose, the precautions mentioned under adrenaline must be observed.

Amphetaminæ Sulphas, $\frac{1}{24}$–$\frac{1}{6}$ gr. (2·5–10 mg.).

Taken by mouth, amphetamine sulphate, in addition to its sympathomimetic effects, exerts a stimulating action on the sensory cortex. It appears to approximate between cocaine and caffeine in pharmacological action, but is probably without the more dangerous habit-forming properties of the former drug. It is employed as a stimulant in narcolepsy and depressive mental states, and has been found useful in alcoholic psychosis, and in some cases of post-encephalitic Parkinsonism, especially in conjunction with preparations containing atropine (*q.v.*) or one of the related alkaloids. Doses of 10 to 40 mg. or more daily may be required in psychotic states. It is claimed that intestinal spasm can be relieved by amphetamine, but the drug is not to be recommended for this purpose. Amphetamine may benefit travel sickness and enuresis. It counteracts the depressant effects of barbiturates, etc., and can be administered to epileptics suffering from the side effects of phenobarbitone. It has recently been given by intramuscular injection in cases of **severe** barbiturate poisoning. It can also be given to combat the withdrawal symptoms of morphine addiction. Idiosyncrasy to the drug is not uncommon, and it may give rise to anxiety, insomnia, temporary mental instability, palpitation, tremor, perspiration, pallor and semi-collapse. An initial test dose of 2·5 to 5 mg. is, therefore, recommended.

Dextro-amphetamine Sulphate (*Dexedrine**).

This differs from the racemic compound amphetamine in having a more sustained cortical stimulant effect and a weaker peripheral action. It is used in depressive states, and in obesity to reduce appetite without inducing irritability.

*Methedrine** (*Desoxyephedrine*).

*Methedrine** is a proprietary derivative of amphetamine. It is issued in 2 mg. tablets and the oral dose is 2–4 mg. until the desired effect is obtained. Its general uses are similar to those of amphetamine, and some authorities consider that in doses of 15–30 mg. intramuscularly or 10–20 mg. intravenously it is the most useful pressor agent available in the treatment of low blood-pressure due to shock or to spinal anæsthesia. Methedrine in doses above 60 mg. may cause restlessness and palpitation. It is also used as a nasal vasoconstrictor with the precautions mentioned under adrenaline. It is also of value in dispelling the lassitude of irradiation sickness.

Cocaina (*q.v.*).

Ephedrinæ Hydrochloridum, ¼–1½ gr.

Ephedrine is an alkaloid obtained from the Chinese plant ephedra. In chemical composition it is related to adrenaline, but is far more stable and it is active by mouth. Qualitatively its action closely resembles that of adrenaline, but its effects are developed far more slowly and are more persistent. A modern theory is that its action *vis-à-vis* adrenaline is analogous to that of eserine and acetylcholine, namely, that ephedrine delays the destruction of adrenaline in the tissues and so prolongs its action. This destruction is normally effected by amine oxidase, and ephedrine prevents this by combining with the latter, an example of the type of substrate competition further considered in the section on chemotherapy on p. 114. Large doses of ephedrine may antagonise adrenaline by combining with the same receptor substances in the effector cells, ephedrine itself having no action on these cells. Ephedrine is used as a nasal vasoconstrictor for similar purposes and with the same precautions as already mentioned under adrenaline, and is less irritant. It is also given in heart-block. Ephedrine is used principally in the treatment of asthma and other allergic conditions. It has the advantage that no tolerance is developed, hence there is no necessity for increasing dosage. During spinal anæsthesia, ephedrine hydrochloride gr. 1 may be injected subcutaneously to prevent, or intravenously to counteract, fall of blood-pressure.[1] Since the sympathetic is motor to the trigonal sphincter and mildly inhibitory to the detrusor muscle, ephedrine may be used to control urinary incontinence due to atony. Following the observation that adrenaline injections have a transient stimulating effect on voluntary muscle, ephedrine has been used orally with some degree of success in the symptomatic relief of *myasthenia gravis*. Headache, palpitations and anxiety may result from ephedrine therapy.

Nebula Ephidrenae Composita B.P.C.

One per cent. ephedrine with menthol, camphor, oil of thyme, in light liquid paraffin. This preparation is used in chronic catarrh, hay fever, etc. It should not be prescribed in acute coryza for reasons contained in the monograph.

Other compounds with a similar composition and action to ephedrine are:

Pseudo-ephedrine.

This is claimed to be more effective than ephedrine in the treatment of asthma in children, the dose being ¼ to ½ gr. It is less toxic and not so powerful a vasopressor as ephedrine.

Propadrine Hydrochloride.

This has a more prolonged action than, and is not so likely to cause anxiety as, ephedrine. The dose is ⅜ to ¾ gr.

Phedracin.*

This substance, distantly related to ephedrine, is used in the treatment of asthma, low blood-pressure following spinal anæsthesia and post-operative shock. It can be given orally, intramuscularly, or intravenously in doses of ½ to 1 gr.

Pholedrine (*Veritol,** *Pholetone**).

Pholedrine is a synthetic sympathomimetic substance isomeric with ephedrine. It has a phenolic hydroxyl instead of the alcoholic hydroxyl of ephedrine, and may, therefore, be regarded as intermediate in structure between adrenaline and ephedrine.

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[1] Ephedrine has an analgesic action which potentiates the action of the spinal anæsthetic.

Pholedrine is thought to act by delaying destruction of adrenaline, and it causes a rise in blood-pressure due to vasoconstriction and by the increased volume output per beat of the heart. This effect is more prolonged but less powerful than that resulting from an injection of adrenaline itself. The drug has a low toxicity and is used for combating marked fall in blood-pressure and respiratory depression associated with surgical shock, spinal anæsthesia, narcotic poisonings and acute infections such as diphtheria. The dosage is 0·75 to 1 ml. of a 2% solution and it is usually administered subcutaneously or intramuscularly. In crises the intravenous route may be used.

Privine.*

*Privine** is an imidazoline derivative with an adrenaline-like action on sympathetic nerve endings. Its vasoconstrictor action is more prolonged than that of adrenaline. It is used as a 1 : 2,000 solution for (*a*) conditions of nasal and sinus congestion with similar precautions to those mentioned under adrenaline; (*b*) conjunctivitis and (*c*) in combination with local anæsthetics to prevent their too rapid diffusion.

Ethylnorsuprarenin.

This is a recently introduced sympatheticomimetic drug which does not raise blood-pressure. It has fewer toxic effects than adrenaline and is used in the treatment of asthma.

Ergota (*q.v.*).

Thyroideum (*q.v.*).

Tuamina.*

Is used as a 1% solution of the sulphate. It constricts the nasal mucosa but has a much weaker systemic effect than ephedrine.

Drugs acting on the Parasympathetic

Acetylcholinæ Hydrochloridum, $\frac{3}{4}$ gr. rising to 3 gr.

As already explained, parasympathetic stimulation communicates itself to the cells by the liberation of acetylcholine at the nerve ends. Subcutaneous injection of the drug produces a powerful vasodilatation which is confined to the arteries and arterioles. It is used, therefore, to relieve arterial spasm, except, of course, that of the coronary arteries. Acetylcholine has no cumulative effect, and its use may be continued for long periods without apparent ill-effect. Owing to its rapid destruction by cholinesterase the effects produced are transient, and therapeutic results are disappointing. The use of carbachol (*q.v.*) is much more promising. By the intramuscular route, acetylcholine has been employed for the relief of paralytic ileus. The drug is ineffective by mouth and is dangerous intravenously owing to the risk of stopping the heart.

Acetylcholine Bromide (*Pragmoline**), 0·1 gm.

Carbacholum (*Doryl**), $\frac{1}{64}$–$\frac{1}{16}$ gr. orally; $\frac{1}{240}$–$\frac{1}{120}$ gr. by subcutaneous injection.

Carbachol is related chemically to acetylcholine. It is, however, much more stable than the latter; in consequence the duration of its action is prolonged and it may be given orally or by subcutaneous or intramuscular injection in aqueous solution. Carbachol may be administered in all conditions where a parasympathetic effect is required, and the only real advantage of parenteral injection over the oral route is the speed with which the required action develops. It is used in auricular, paroxysmal tachycardia, arteriospasm and as a stimulant in post-operative atony of the intestine (paralytic ileus) or of the bladder with retention of urine. Applied to the conjunctiva, a 0·75% aqueous solution has a miotic action and reduces intraocular tension.

Mecholyl* (acetyl-β-methylcholine chloride), 3–7½ gr. orally; 0·025 G. subcutaneously.

*Mecholyl** is a compound related to carbachol and possessing similar therapeutic indications. It acts more vigorously than carbachol on the cardiovascular system and is often preferred in the treatment of auricular paroxysmal tachycardia. On the gastro-intestinal tract carbachol has the more pronounced action.

Neostigmine (*Prostigmine**).

Neostigmine (0·5–2·5 mg.) is a synthetic body comprising a modification of the molecular structure of physostigmine. It has a similar action to the naturally-occurring drug, but is stable in solution, and has a lower toxicity. Apart from its action in inhibiting cholinesterase and so preventing the destruction of acetylcholine, its effect in *myasthenia gravis* may be due to its inhibiting a curare-like substance responsible for the symptoms. It is given by subcutaneous or intramuscular injection in post-operative ileus and retention of urine, in megacolon and as a stimulant to voluntary muscle in *myasthenia gravis*. For the latter disease an initial dose of 2 mg. is given subcutaneously and this is repeated at sufficiently frequent intervals or increased to an amount necessary to control symptoms. It is often advisable to use the concentrated solution (2·5 mg. in 1 ml.), and it is combined with atropine to avoid griping, salivation and bradycardia. Facial fibrillation is the first sign of overdosage. In severe cases it may be given by intravenous drip at the rate of 1·5 to 3 mg. per hour. As an alternative to parenteral administration in *myasthenia gravis*, the drug can be given orally as tablets of 15 mg. Neostigmine bromide 15 mg. thrice daily by mouth has been used to supplement parenteral therapy. The action of neostigmine in *myasthenia gravis* can be enhanced by potassium chloride (5–10 gm. daily), ephedrine and guanidine hydrochloride given in 2 gr. tablets. See also D.F.P. below. Neostigmine is sometimes employed to improve neuromuscular function in dysfunction due to trauma, poliomyelitis, bulbar palsy and rheumatoid arthritis. It may be used as an antidote in atropine poisoning.

Neostigmine Methyl Sulphate.

Neostigmine Bromide.

Injectio Neostigminæ Methylsulphatis, Off.

Physostigminæ Salicylas (Eserine Salicylate), $\frac{1}{100}$–$\frac{1}{50}$ gr.

The action of acetylcholine is transient owing to its destruction by cholinesterase present in the tissues. Physostigmine appears to retard this destruction, hence its effects simulate parasympathetic stimulation. In therapeutic doses the smooth muscle of the intestine is chiefly affected, and the drug is administered in paralytic ileus. Larger doses cause bronchial spasm and bradycardia. The concurrent injection of acetylcholine enhances the effects. Applied to the conjunctiva, physostigmine constricts the pupil and reduces intraocular pressure, and it is used in ophthalmology in 1% solution to relieve glaucoma. Centrally its action is mainly depressant. Other preparations include the alkaloid itself, the sulphate and the amino-oxide (*Geneserine**) which is less toxic.

Pilocarpinæ Nitras, $\frac{1}{20}$–$\frac{1}{6}$ gr.

Pilocarpine closely simulates parasympathetic activity probably by acting like acetylcholine directly on the tissues involved. In small doses it chiefly affects the glands and is sometimes employed for its marked diaphoretic action. It is now principally used for its action on the eye, which is similar in effect to that of physostigmine.

Di-isopropyl-fluoro-phosphate (D.F.P.).

This compound, although chemically not related to physostigmine or neostigmine, inhibits cholinesterase like these substances, but this inhibition with D.F.P. is permanent and irreversible, whereas with the other compounds it is temporary. Like physostigmine and unlike *Prostigmine*, it is a central excitant and facilitates excitatory transmission in the spinal cord and medulla. It is much less effective than *Prostigmine* in antagonising curare. It is a colourless, oily liquid, and for therapeutic purposes a 0·05 to 0·2% solution dissolved in olive oil is employed in the following conditions: (1) In *myasthenia gravis* it is less effective than *Prostigmine* but its more prolonged action might make it a useful supplement to the latter drug. It is given intramuscularly in doses of 0·5 to 2·0 mgms. daily. (2) In paralytic ileus, intramuscular injection of the drug appears to be more effective than *Prostigmine** or posterior pituitary extract. Its effects can be neutralised by atropine. (3) It is also applied locally to the eyes in cases of glaucoma, where it causes myosis and decreased intraocular tension. Its effects are much more potent and persistent than physostigmine, and may succeed where this has failed. It neutralises the effect of atropine on the eye.

Toxic symptoms include bradycardia, salivation, vomiting and diarrhœa, due to parasympathetic stimulation.

Meprochol (*Esmodil).**

*Esmodil** is an 0.3% solution of trimethyl-methoxy-propanyl ammonium bromide, and is used as a parasympathetic nerve stimulant in doses of 1 mil.

Furfuryl trimethyl ammonium chloride (*Furmethide*).

This is a recently synthesized parasympatheticomimetic drug acting particularly on the bladder when this is paralysed. The subcutaneous dosage is 1·25 to 3 mg. in children under 10, and 5 to 7 mg. in adults.

The Tropine Alkaloids

The peripheral action of the tropine alkaloids has been demonstrated to be a temporary desensitisation of the cells to the action of acetylcholine. The action of these bodies, therefore, resembles a partial paralysis of the parasympathetic nerve ends, and formerly this was held to be the mechanism by which their effects were produced. Their peripheral actions, which are described under atropine sulphate, are qualitatively identical, but they differ in regard to their central action. The following table illustrates the distribution of these alkaloids amongst the principal crude drugs in which they occur:

Atropine.	Hyoscyamine.	Hyoscine.
B	elladonna.	
H	yoscyamu	s.
St	ramoniu	m.

The extent to which the name of the drug encroaches to the right or to the left of the central column gives a rough diagrammatic indication of the extent to which the alkaloids named are present in the drug. The medicinal properties of the above drugs are virtually identical with those of their principal alkaloid hyoscyamine (*q.v.*).

The following are their chief preparations:

Belladonna Pulverata, Off. $\frac{1}{2}$–3 gr.
Standardised, powdered belladonna leaf.

Emplastrum Belladonnæ, Off. An analgesic plaster.

Extractum Belladonnæ Siccum, Off. $\frac{1}{4}$–1 gr.

Linimentum Belladonnæ, Off.
An analgesic liniment for joint pains, sprains, etc.

Suppositorium Belladonnæ, Off.

Tinctura Belladonnæ, Off. 5–15 min.

Extractum Hyoscyami Siccum, Off. $\frac{1}{4}$–1 gr.

Tinctura Hyoscyami, Off. (U.S.P. sim.), $\frac{1}{2}$–1 fl. dr.

Extractum Stramonii Liquidum, Off. $\frac{1}{2}$–3 min.

Extractum Stramonii Siccum, Off. $\frac{1}{4}$–1 gr.; in post-encephalitic and similar conditions, 1–8 gr. t.d.s.

Tinctura Stramonii, Off. 5–30 min.

Atropinæ Sulphas, B.P., $\frac{1}{240}$–$\frac{1}{60}$ gr.

Atropine (*dl*-hyoscyamine) is an optical isomer of hyoscyamine (*q.v.*), from which it is prepared artificially; only a trace of atropine occurs in galenical preparations of belladonna, probably none in the fresh herb. It may be administered orally or by parenteral injection. The following synopsis of its principal actions should be preceded by a mental review of the parasympathetic ramifications in order that the relationship between this innervation, and the effects produced by the drug, can be clearly comprehended. It will be apparent that the actions are mainly referable to smooth muscle and the glands. Applied topically or given internally, atropine dilates the pupil of the eye, and, by consequent distortion of the spaces of Fontana and pressure on Schlemm's canal, causes a sharp rise in intraocular tension. It is used to dilate the pupil, especially in children, for ophthalmological examination, but possesses the enormous disadvantage that accommodation, etc., may take a week to return to normal. It may be used in iritis to rest the eye, relieve pain and prevent synechiæ from forming; accommodation and reaction to light are both paralysed. Salivary and bronchial secretion are diminished, also the gastric secretion (see below). Perspiration is checked because the sweat glands employ the acetylcholine stimulus, but the skin vessels are dilated, the skin becoming dry and flushed. Idiosyncrasy, which is not uncommon, or overdosage may produce an erythematous rash. By inhibition of vagal influence the heart rate may be increased. The bronchial muscle is relaxed, also the smooth muscle of the uterus, bladder, pyloric sphincter and gut when in spasm. Larger doses, however, possibly by stimulating Auerbach's plexus, may produce purgation. The sphincters are somewhat relaxed. Vagal inhibition is said to result in constriction of the visceral blood-vessels, but no appreciable rise in blood-pressure follows owing to the compensatory dilatation of the vessels of the skin. Applied in such a form as to penetrate the skin, atropine depresses the sensory nerve ends and relieves pain (*cf.* Liniment of Belladonna).

In consequence of the actions outlined above, atropine, and the drugs containing tropine alkaloids, are employed to reduce excessive secretion in hyperidrosis, acute rhinitis, gastric hypersecretion, etc., to relieve the paroxysms of bronchial asthma, whooping-cough, biliary colic, pylorospasm and dysmenorrhœa, to rest the bladder in acute cystitis and to relieve vesical spasm resulting in enuresis. Small doses are added to violent cathartics to prevent griping. Post-encephalitic Parkinsonism is treated by one or another of the tropine alkaloids or preparations of the drugs which contain them; relief of the rigidity but not of the tremor being mainly obtained. In addition to its peripheral effects, atropine has a powerfully stimulant action on the central nervous system followed, later, by depression. The motor areas of the brain are first affected, then the sensory areas. Large doses may give rise to tremor followed by hallucinations, delirium and convulsions. Death occurs by paralysis of the respiratory centre. In smaller doses, however, atropine stimulates this centre and it is used in the treatment of narcotic poisoning as a respiratory stimulant. By antagonising the action of acetylcholine it is specific for cases of poisoning by muscarine, physostigmine or pilocarpine. The pre-operative injection of atropine sulphate is advisable for a number of reasons:

1. The respiratory centre is stimulated; this is especially important when morphine is used. (See under Morphine.)
2. It checks vagal inhibition of the heart (chloroform anæsthesia).
3. It checks bronchial secretion (ether anæsthesia).
4. It dilates the bronchi, thus improving the airway and promoting the absorption of a volatile anæsthetic.
5. By constricting the splanchnic vessels it reduces risk of collapse.
6. If morphine is used, atropine may diminish intestinal spasm and prevent vomiting.

The following table shows the resemblances and differences between acute poisoning by the drugs named and the condition of acute mania:

	Motoric Disturbance.	Salivation.	The Eye.	The Skin.
Alcohol ..	Tremor, restlessness	Mildly increased	Some pupillary dilatation	Moist red
Atropine ..	Convulsions	Inhibited	Wide dilatation (non-reactive to light)	Dry red
Cocaïne ..	Do.	Do.	Dilatation	Moist pale
Mania	Great restlessness	Profuse (drooling)	Do. (but light reflex remains)	Moist flush
Physostigmine Pilocarpine Muscarine	Do. Also vomiting and diarrhœa (these may occur with cocaine)	Do.	Constriction	Moist pale

Lamella Atropinæ, Off. Discs for eye medication.

Oculentum Atropinæ, Off. Atropine eye ointment is used to rest the eye, relieve pain and prevent adhesions in iritis, etc.

Oculentum Atropinæ cum Hydrargyri Oxido, Off. This is a suitable antiseptic and analgesic application to the eyelid margins for the relief of styes.

Atropinæ Methylnitras (*Eumydrine**), $\frac{1}{60}$–$\frac{1}{30}$ gr.

Atropine methylnitrate is a powerful mydriatic, but the duration of its action is much shorter than in the case of atropine and the drug is less toxic. Its principal use, however, is in the treatment of congenital pyloric stenosis. Best results are obtained by permitting the drug to be absorbed from the mouth, and as solutions are unstable, it is convenient to prepare *lamellæ* (glycerin-gelatin discs normally used for ophthalmic medication), each containing a dose suitable for an infant, which can be placed under the tongue about 20 minutes before feeding, six or seven times a day. The usual dosage is from $\frac{1}{300}$ to $\frac{1}{120}$ grain, but some authorities use larger and others much smaller doses. Treatment is continued until the subject has not vomited for a week or more.

Homatropinæ Hydrobromidum, $\frac{1}{64}$–$\frac{1}{32}$ gr.

Homatropine is a synthetic base related to atropine. It is largely used in eye examinations to dilate the pupil, since the effect develops rapidly and is transient. Its systematic action resembles that of atropine, but varies considerably with the subject and the drug is seldom used internally.

Lamella Homatropinæ, Off. Uses similar to atropine discs.

Hyoscinæ Hydrobromidum (Scopolaminæ Hydrobromidum), $\frac{1}{200}$–$\frac{1}{100}$gr.

The peripheral effects of hyoscine, although identical with those of hyoscyamine, are transient in duration. Centrally, the action is powerfully depressant. The motor areas of the brain are primarily affected; larger doses depress, also, the sensory areas and produce sleep. Administered by injection, the action of the drug is quickly developed and hyoscine is a most rapidly acting hypnotic. It is used to control the paroxysms of acute mania. Hyoscine has been termed the "truth drug," since its employment tends to remove inhibitions and may encourage garrulous candour, especially if administered in conjunction with morphine. This combination is still sometimes employed in the "twilight sleep" method for anæsthesia in parturition. It must be remembered, however, that both morphine and hyoscine depress the respiratory centre, and their concurrent use is not unattended by risk. On this account it is better and more usual to employ papaveretum (*q.v.*) rather than morphine, with hyoscine for pre-operative sedation, etc. Hyoscine in increasing dosage is largely employed in the maintenance treatment of post-encephalitic Parkinsonism; encephalitics appear to be able to tolerate relatively enormous doses of the drug. To combat its depressant action on the respiratory centre it is often combined with strychnine in these cases, while pilocarpine has also been used with the idea of antagonising the unwanted peripheral actions of hyoscine. It is not inappropriate to comment that the control of the rigidity of Parkinsonism effected by hyoscine can hardly be attributed to its normal depressant action on the motor cortex. Atropine, which is a central stimulant, and hyoscyamine, which, in therapeutic doses, has little action centrally, have both been successfully employed in the same type of disturbance. We must assume, therefore, that the encephalitic reacts in some special, and quite unexplained, way to the tropine alkaloids. Hyoscine is employed to control sea-sickness and can be given for several days for this purpose. An early morning dose of $\frac{1}{100}$ gr. is followed by two doses of $\frac{1}{200}$ gr. later in the day. Individual idiosyncrasy to hyoscine may result in violent excitement preceding the normal sedative action on the cortex. Because of its transient action it is preferred in adults for mydriasis. It is less powerful than atropine but less likely to cause glaucoma, possibly because of the shorter duration of action.

Hyoscyaminæ Sulphas, $\frac{1}{200}$–$\frac{1}{100}$ gr.

l-Hyoscyamine is the principal alkaloid in Solanaceous plants. From it atropine (*dl*-hyoscyamine) is prepared by racemisation with an alkali. Like atropine, its main peripheral action is to minimise tissue response to acetylcholine and related drugs, and in this respect it is approximately twice as powerful as atropine. Centrally, however, it has little effect except in large doses, when again its action is identical with that of atropine. It is given in doses of $\frac{1}{120}$ gr. b.d. in peptic ulcer.

E 3 (Benzilic ester of hydroxymethyl-dimethyl-ethyl ammonium chloride).

This compound is used as a 1% solution as a mydriatic. It has been found of value in cases showing atropine irritation of the eyelids when this has been used as a mydriatic. It is more powerful than homatropine but less so than atropine, and requires to be given more frequently than the latter.

Trasentin.*

*Trasentin** is a complex organic compound with a pharmacological effect similar to atropine in the abolition of spasm of smooth muscle but, unlike atropine, it has no pronounced action on the pupils, heart or salivary glands. It is given for the relief of pylorospasm, intestinal colic, spastic constipation, dysmenorrhœa, and renal and biliary colic. The dose is 75 to 150 mg., and the drug can be given by mouth, rectally, or intramuscularly.

DRUGS INFLUENCING DIGESTION

Acids and Alkalis (*q.v.*).

Enterogastrone.

This is a substance produced by making an extract of intestinal mucosa which has been in contact with fat. It inhibits gastric secretion by a humoral mechanism related to the type of inhibition which occurs as the result of fats in the intestine. This substance and a similar compound, urogastrone, found in normal urine, have been used in the treatment of peptic ulcer. Gastroduodenal extracts orally or by injection have also been used for this purpose, and it is considered likely that normal gastric and duodenal function is maintained by active substances of this type present in healthy mucosa and that their absence predisposes of peptic ulcer.

Acidum Hydrocyanicum Dilutum, Off. 2–5 min.

Dilute hydrocyanic acid has a sedative action on sensory nerve ends. It is given internally, often in conjunction with alkalis to check vomiting and relieve gastric pain.

Bitters

Many drugs exert a bitter taste in the mouth and, by exciting the Pavlov reflex, give rise to salivation and increased gastric secretion (*e.g.* Strychnine, Quinine). Under this heading, however, are here included only those commonly prescribed drugs which act on account of their bitterness and have little or no other pharmacological effect.

Aurantii Cortex (Bitter Orange Peel).

Infusion Aurantii, B.P.C. ½–1 fl. oz.

Tinctura Aurantii, Off. ½–1 fl. dr.

Syrupus Aurantii, Off. ½–2 fl. dr.

Calumba (a root).

Calumba contains no tannins, and its preparations are, therefore, compatible with ionising salts of iron.

Infusum Calumbæ, B.P.C. ½–1 fl. oz.

Cinchona (a bark).

Cinchona is not a pure bitter, but is included here because its galenical preparations are used chiefly as bitters. Specific effects are discussed under quinine, quinidine and totaquine.

Tinctura Cinchonæ Composita, B.P.C. ½–1 fl. dr.

Gentiana (root and rhizome).

Gentian is an aromatic bitter. It is used mainly as the infusion which contains also bitter orange and lemon peel.

Infusum Gentianæ Compositum Concentratum, Off. 30–60 minims.

Quassia (a wood).

Like calumba the preparations of quassia are compatible with ionised iron.

Infusum Quassiæ, B.P.C. ½–1 fl. oz.

Taraxacum (Dandelion root).

In larger doses this acts as a laxative and it had, formerly, a reputation as a cholagogue.

Succus Taraxaci (Taraxacum juice), **B.P.C.,** ½–2 fl. dr.

Cholagogues

Cholagogues are substances used to promote the flow of bile into the intestine. Whole bile, or the bile salts, when administered by mouth stimulates the liver to increased bile secretion, other substances such as magnesium sulphate, certain foodstuffs like oils and fats, and products of protein digestion, *e.g.* peptone, give rise to gall-bladder contraction by reflex from the duodenum and relaxation of the sphincter of Oddi. The increased drainage of the gall-bladder which thus results is useful in chronic inflammation of the organ. Whilst the natural bile salts produce true choleresis and increase both the volume and constituents of bile the oxidation product, dehydrocholic acid, increases bile volume but reduces the solid constituents, thus diluting the bile (dehydrocholeresis). Bile salts stimulate the intestinal tract. Solutions of bile are lytic to pneumococci and hæmolyse red cells. Occasional toxic symptoms from bile salts are bradycardia and twitchings. Oral preparations are employed: (1) to aid in removing small biliary calculi and may be combined with anti-spasmodic drugs like atropine for this purpose; (2) to facilitate biliary drainage and prevent ascending infection in cholecystitis and cholelithiasis; (3) in obstructive jaundice, given with vitamin K, they help absorption of the latter and reduce the hæmorrhagic tendency. Bile salts also assist in the absorption and digestion of fats. Intravenously dehydrocholic acid is used: (1) to outline bile ducts at operation; (2) in cholecystography, to hasten appearance of the gall-bladder shadow and elimination of iodophthalein, (3) to estimate the circulation time (arm to tongue), a bitter taste indicating the arrival of the drug at the tongue.

Fel Bovini (ox bile).

Ox bile given orally increases production of bile by the liver. It is used in chronic inflammation of the gall-bladder, to promote fat digestion and absorption and diminish intestinal putrefaction. Ox-bile enema is used to stimulate a sluggish colon and relieve flatulent distension. The following is a suitable formula:

℞	Ext. Fel. Bovini	ʒi
	Ol. Terebinth.	ʒiv
	Sapo. Moll.	ʒii
	Glycerin	ʒiv
	Aq.	ad Oi
	m.s.a.	ft. enema.

Extractum Fellis Bovini, Off. 5–15 gr.

Extract of ox bile is the preparation normally employed for oral medication (in pill form) or for enemata.

Sodii Tauroglycocholas, B.P.C. (Bile Salts), 2–6 gr.

Bile salts, consisting chiefly of a mixture of sodium taurocholate and sodium glycocholate, are used, chiefly in the form of capsules, for oral medication instead of bile extract.

Dehydrocholic Acid (Dehydrocholin), for oral medication. 4–8 gr.

Sodium Dehydrocholate, for intravenous medication. 5–10 mil. of a 20% solution.

Magnesii Sulphas (*q.v.*).

Oleum Olivæ (*q.v.*).

Peptonum, B.P.C., 5–15 gr. (by mouth).

Peptone is a mixture of substances obtained by the partial hydrolysis of protein. It is given by mouth in conjunction with magnesium sulphate to promote the flow of bile. In doses of 0·3 ml. rising to 1·5 ml., in 7·5% solution, it is injected intramuscularly for non-specific desensitisation in some cases of allergy, *e.g.* asthma, urticaria. For intravenous therapy similar volumes of a 5% solution are employed. It is a component of certain bacteriological media. Other substances used for non-specific desensitisation, in initially minute but increasing dosage, include whole milk, whole blood, tuberculin and "T.A.B." vaccine. Some of these, in larger dosage, are used for "shock" therapy.

Hæmoprotein.*

*Hæmoprotein,** prepared by peptic digestion of ox-blood fibrin, is given by injection for non-specific protein therapy in allergic conditions. *Lertigon,** a histamine protein complex, is employed similarly to the above.

Carminatives

Carminatives are substances used to assist the expulsion of flatus and reduce griping. Many of them are aromatic or spice-like in character and appear to act by promoting local movement of the tract. Carminatives described elsewhere include volatile oils, alcohol, ether and charcoal.

Capsicum (a fruit).

Capsicum contains pungent rubefacient principles which, in small doses, act as carminatives. The tincture is used in the withdrawal treatment of alcoholic addiction, to simulate the warming action of alcohol on the stomach. Preparations of capsicum for external use are applied to unbroken skin to exert a rubefacient and counter-irritant effect.

Gossypium Capsici B.P.C. (Capsicum wool, *Thermogene,** sim.).

This consists of cotton-wool impregnated with capsicum.

Tinctura Capsici, Off. 5–15 min.

Tinctura Capsici Fortior, B.P.C.

A stimulating application for external use.

Carbo Ligni (Charcoal), *q.v.*

Cardamomum (a seed).

Cardamom seed contains an aromatic volatile oil, and preparations containing cardamom are widely used for their carminative action in the treatment of colic, and for the prevention of griping by purgatives.

Tinctura Cardamomi Composita, Off. ½–1 fl. dr.

This is a pleasantly aromatic tincture used against colic and as a flavouring agent in mixtures.

Zingiber (Ginger root).

Ginger root contains pungent, aromatic bodies which exert a carminative action on the tract. Preparations of ginger are used to expel flatus and relieve colic, and to cover the taste of other medicaments.

Syrupus Zingiberis, Off. ½–2 fl. dr.

Tinctura Zingiberis Fortis, Off. 5–10 min.

Digestive Ferments

Diastasum (*Taka-Diastase,** sim.), 1–5 gr.

Diastase is a ferment which converts starch into monosaccharide sugar and so allows of its assimilation. Its optimum activity is at pH 5·2; media more acid or alkaline in reaction decrease or completely inhibit its activity. Diastase is administered in cases of amylaceous dyspepsia and is best given after meals, preferably with magnesium carbonate to diminish gastric acidity.

Extractum Malti, 1–4 dr.

Extract of malt is a brown, viscous liquid obtained from malted barley grain. It is a nutritive substance containing carbohydrate, the vitamin B complex and a little diastase.

Extractum Malti cum Oleo Morrhuæ, Off. 1–4 dr.

Extract of malt with cod-liver oil is used as a nutriment, especially for undernourished children and in wasting diseases. The malt extract covers to some extent the fishy taste of the oil.

Pancreatinum, 3–10 gr.

Pancreatin contains the mixed ferments present in the external secretion of the pancreas—viz. trypsin, lipase and amylase. It is usually obtained from the pig or the ox and occurs as a whitish or buff-coloured powder with a meat-like smell. The pancreatic ferments are inactivated by acids, and pancreation is best administered about two hours after meals in conjunction with sodium bicarbonate and magnesium carbonate.

℞ Pancreatin
Sodii Bicarb.
Mag. Carb. Pond. .. .. ana gr. v
ft. oblat.

It is given to assist the digestion of protein and starches, especially in the case of invalids and the aged. Pancreatin, together with sodium bicarbonate, is used for predigesting milk, farinaceous foods and beef-tea for convalescents. "Peptonising powders" are available commercially for these purposes.

Papainum, 2–10 gr.

Papain is a dried plant juice possessing considerable proteolytic activity which it exerts in both acid and alkaline media. It is used in digestive disorders associated with faulty protein digestion and may be prescribed in mixture form or as a cachet.

Pepsinum.

Pepsin is the proteolytic enzyme found in the human stomach and that of certain other mammals. It is active only in an acid medium (optimum concentration 0·4% HCl). It is administered in conditions of pepsin deficiency associated with achylia, usually in mixture form combined with dilute hydrochloric acid, *e.g.*:

℞ Pepsin. .. .. .. gr. v
Ac. Hydrochlor. Dil. }
Syr. Zingib. } .. āā ♏.xv
Aq. Chlorof. .. .. ad ℥ſs.
ft. mist. pro dos.

Rennin.

Rennin is used in the preparation of junket and whey; 1 gr. will curdle 3 pints of milk.

APERIENTS

Substances used to promote evacuation of the bowels are termed variously aperients, cathartics, laxatives or purgatives, and with the exception of the word "laxative," which by usage implies a mildness of action, the terms are used interchangeably. Aperients are divided into various groups according to their chemical relationships and modes of action.

Anthracenes (Anthraquinones).

The members of this group contain active principles related to the coal-tar product, anthracene. These substances are absorbed from the small intestine and are excreted mainly into the large intestine, where they exert a stimulating action directly on the muscle fibres, producing purgation after six to eight hours. They do not, in general, irritate the mucous lining of the intestine. The more important members of this group are:

Aloe, 2–5 gr. (a dried plant juice).

Aloes contain a proportion of irritant resin in addition to its anthracene-purgative content, hence it produces some evacuation of the small intestine by irritation of the mucous membrane. It is a powerful drug very liable to cause griping and congestion of the pelvic blood-vessels. It is, therefore, contraindicated in pregnancy and when hæmorrhoids are present. Combined with iron it is used in functional amenorrhœa, since large doses have been shown to exert some tonic action on uterine muscle. Absorption of the drug is indicated by urinary pigmentation, and by its appearance in the milk of lactating women, whence it is liable to affect a feeding infant. Aloin, an impure mixture of crystalline principles extracted from aloes, is inferior to the parent drug in action, but its reduced bulk renders it convenient for pills, etc.

Pilula Aloes, Off. 4–8 gr.

Pilula Aloes et Ferri, Off. 4–8 gr.

Cascara Sagrada (a bark).

This is a typical anthracene purgative. It is administered, sometimes in conjunction with nux vomica, in intestinal atony and chronic constipation. Evacuation occurs some eight hours after administration:

℞	Elixir Cascar. Sag.	♏xx
	Tinct. Nuc. Vom.	♏x
	Syr. Zingib.	♏x
	Aq. Cinnam.	ad ℥ss
	ft. mist.	pro dos.

℞	Ext. Cascar. Sag. Sicc.	gr. ii
	Ext. Bellad. Sicc.	gr. ⅛
	Ext. Ipecac. Liq.	♏⅛
	ft. pil.	pro dos.

Elixir Cascaræ Sagradæ, Off. 30–60 min. (*Cascara Evacuant,** sim.).

Extractum Cascaræ Sagradæ Siccum, Off. 2–8 gr.

Rheum (Rhubarb; a peeled root), 3–15 gr.

In addition to its aperient principles, rhubarb contains aromatic substances and tannic acid. It is used in small doses to relieve gastric distension and stimulate digestion. In larger doses its use should be restricted to the promotion of a brisk purge in mild food-poisoning, etc., since the initial evacuation is followed by the constipating action of its tannic acid content. It is, therefore, strongly contraindicated in chronic constipation.

As a digestive stimulant:

℞ Pulveris Rhei ..	.. gr. ii
Tinct. Card. Co. Sp. Ammon. Arom.	.. āā ♏xx
Aquam. Menth. Pip.	.. ad ℥ss
ft. mist.	pro dos.

Pilula Rhei Composita, Off. 4–8 gr.

Pulvis Rhei Compositus, Off. (Gregory's Powder), 10–60 gr.

This contains rhubarb, magnesium carbonate and ginger.

* * * * * *

Chrysarobinum.

Chrysarobin is a yellow powder of vegetable origin containing, amongst other ingredients chrysophanolanthranol, which is related to the anthracenes. It is applied externally as an ointment or pigment, as a stimulant in psoriasis and as a parasiticide in tinea. In treating psoriasis it is usual to apply the ointment until a definite dermatitis is produced, then to remove it with a bland oil and apply zinc oxide ointment. Applied over a large area absorption may occur and give rise to renal irritation. It should be kept away from the eyes. Stains on linen produced by chrysarobin can be bleached by a solution of chlorinated lime.

Pigmentum Chrysarobini, B.P.C.

Contains chrysarobin in a solution of gutta-percha. It is applied and allowed to dry on the skin. This preparation is more cleanly in use than ointments.

Unguentum Chrysarobini, Off.

Dithranol, B.P.C. (*Derobin,* Cignolin**).

Dithranol is dihydroxyanthranol, which is related to the active principles of chrysarobin. It is more uniform in composition than the latter and possesses some four times the therapeutic activity, but is less toxic. It is used for the same purposes as chrysarobin. The following is a suitable application:

℞ Dithranol ..	.. .. 2%
Paraff. Molle. Paraff. Liq.	.. .. āā p. æq.
ft. ung.	apply twice a day.

* * * * * *

Senna (pods and leaves).

The action of senna is almost identical with that of cascara, but it does not contain the bitter lactone present in the latter drug and, prior to the introduction of the elegant *Elixir Cascaræ Sagradæ*, senna was often preferred on account of its less objectionable taste. In habitual constipation, patients often discover for themselves what number of senna pods is necessary for daily relief, and it is customary to infuse the requisite number overnight and drink the resulting *tisane* before breakfast on the following morning.

Confectio Sennæ, B.P. (Senna Jam), 1–2 dr.

Infusum Sennæ, B.P., ½–2 fl. oz., used as a vehicle for aperient mixtures.

Mistura Sennæ Composita, B.P., 1–2 fl. oz. (Black Draught, " Salts and Senna "), contains also magnesium sulphate and carminatives.

Syrupus Sennæ, B.P. (U.S.P. sim.), ½–2 fl. dr.

Phenolphthaleinum, 1–5 gr.

Phenolphthalein is an artificially prepared substance very distantly related in structure to the anthracenes, but similar thereto in pharmacological action. It produces watery stools six to eight hours after ingestion and the action is confined to the large intestine. It is a suitable aperient in pregnancy and may be prescribed in tablet form, or as an emulsion with, or suspension in, liquid paraffin. Phenolphthalein should not be administered over a prolonged period as it is cumulative and may give rise to skin rash. Following its absorption a proportion of the drug appears in the bile, sometimes causing additional evacuations on this account. This excretion in the bile is especially interesting as providing the rationale for the use of its iodised derivative (*vide infra*).

Iodophthaleinum (Tetra-iodophenolphthalein).

This is given intravenously or, with special precautions, by mouth, and, being opaque to X-rays and excreted with the bile, it provides an excellent contrast medium in cholecystography. The intravenous dose is ⅓ to ½ grain per lb. body-weight, up to 75 grains in 10% sterile aqueous solution.

Dihydroxyanthraquinone (*Istin**).

This is a synthetic purgative related to the anthracenes. The dosage is 2–6 gr.

Drastic Purgatives

The drastics, or hydragogue cathartics, comprise such substances as **Colocynth** (a dried fruit pulp), **Jalap** (a root), **Podophyllin** (a resin), and **Scammony** (a stem).

No individual description of these drugs is necessary since their mode of action is similar. The cathartic effect is produced by irritation of the intestinal mucosa, which augments the short reflexes through Auerbach's plexus. In other than small doses, bloody stools may result and, invariably, a mild degree of enteritis is produced which causes the outpouring of fluid into the lumen of the gut. For this reason they were, formerly, much used in œdematous conditions to drain the waterlogged tissues. Their use is contraindicated in inflammatory, ulcerative and hæmorrhoidal conditions of the bowel, or for habitual constipation. They have no direct cholagogue effect.

Pilula Colocynthidis et Hyoscyami, Off. 4–8 gr.

Pulvis Jalapæ Compositus, B.P.C. 10–60 gr.

This preparation is prescribed for œdematous patients.

Podophyllin, 25% solution suspension in oil by local application has been found useful against condylomata acuminata.

Oils

The members of this group possess no uniformity of action, but they are grouped together for convenience.

Paraffinum Liquidum, ¼–1 fl. oz.

This hydrocarbon product of petroleum distillation is not absorbed to any appreciable extent from the intestine, and its action is purely that of a lubricant. It is liable to cause seeping from the anus, and to minimise this untoward effect it can be administered in combination with soft paraffin as the following viscous liquid:

℞ Paraff. Molle Alb. .. ʒi
Olei Menth. Pip. .. ♏i
Paraff. Liquidum .. ad ℥ss
pro dos.

The aromatic oil is included to disguise the bland, insipid flavour. Emulsions of liquid paraffin are devised for the same purpose. It has been established that the regular use of liquid paraffin interferes with the absorption of carotene and may give rise to deficiency of the oil-soluble vitamins.

Emulsio Paraffini Liquidi Composita (*Red Label Petrolagar,** sim.), 1–4 fl. dr., an emulsion of liquid paraffin with phenolphthalein.

Emulsio Paraffini Liquidi (*Petrolagar,** sim.), 1–4 fl. dr., frequently used for children and in pregnancy.

Oleum Olivæ (*q.v.*).

Oleum Ricini, B.P., 1–4 fl. dr.

Castor oil is composed in the main of glyceryl ricinoleate; it has emollient properties which are used in ophthalmic practice and for application to the skin. Taken internally, it is split in the intestine by lipase to glycerin and alkali ricinoleate, and the latter exerts a mildly irritant action on the mucosa which provokes efficient and painless evacuation of both the small and large intestine. Its action is reasonably rapid, and the drug is used in food-poisoning and as an adjunctive in the medical induction of labour. On account of its nauseous taste it is sometimes administered in capsules, as an emulsion, or floating on fruit juice.

Mercurial Aperients

Hydrargyri Subchloridum (Calomel), ½–3 gr.

Owing to its extremely insoluble nature, calomel taken internally has a very low toxicity in comparison with mercuric chloride (hydrargyri perchloridum, *q.v.*), and it is non-corrosive to the alimentary mucosa. In small doses it is used as an intestinal antiseptic and indirect cholagogue, and it exerts an aperient action (drastic in those possessing an idiosyncrasy to mercury) by its mildly irritant properties, which give rise to increased mucus secretion and reflexly increase peristalsis. It is excreted partly unchanged and partly as sulphide by the bowel, but small quantities become soluble and are absorbed, probably as proteinate, and exert a diuretic action (see under Mersalyl). Children usually tolerate mercurial aperients well, but in most cases it is advisable to follow an overnight dose of a mercurial by salts in the morning to ensure complete elimination from the tract.

Hydrargyrum (Mercury), ½–3 gr.

Small doses of metallic mercury in a fine state of subdivision taken internally possess an action akin to that of calomel. For adults the official pill, and for children Mercury with Chalk, are commonly prescribed. They both exert a milder purgative effect than calomel, but appear to be better absorbed, hence the diuretic action may be more marked. Mercury with Chalk is often prescribed in half-grain repeated doses in the mercurial treatment of syphilis. The further actions of mercury are discussed under appropriate sections.

Hydrargyrum cum Creta, Off. (Grey Powder), 1–5 gr.

Pilula Hydrargyri, Off. (Blue Pill), 4–8 gr.

Bulk-forming Aperients

A number of vegetable substances possess the property of swelling considerably in the presence of water, and forming soft, gelatinous masses which pass through the alimentary tract unabsorbed. If administered orally in the dry state, usually as granules, they cause retention of water in the lumen of the gut, the increased bulk stimulating peristaltic action and the passage of soft stools. They are to be avoided in spastic constipation, in obstruction and pronounced intestinal atony. The following are often used:

Agar (a dried seaweed product), 1–4 dr.

Ispaghula (Spogel Seed), 45–150 gr.

Psyllium (a seed), about 1 oz.

*Normacol** is a granular preparation of bassorin possessing unusual bulk-forming properties. It contains, also, some frangulin (an anthracene aperient) to assist peristalsis.

*Isogel** is a granular preparation of dried mucilaginous seeds which acts in a similar way to the above.

Saline Purgatives

These are soluble salts which, administered in aqueous solution preferably well diluted, do not readily diffuse through the intestinal epithelium. The bulk in the lumen of the gut is consequently augmented, and, in sufficient dosage, this increased bulk stimulates peristaltic movement. Small doses of these salines tend to render the intestinal contents more fluid and may promote the absorption of toxins. When strong solutions are administered, drainage of water from the tissues into the gut occurs by osmosis. Taken when the stomach is empty an aperient action occurs in about two hours.

Magnesii Sulphas, ½–4 dr.

Epsom Salts is a commonly used saline purgative possessing a bitter taste. By reaction with the intestinal bicarbonate a certain amount of sodium sulphate is formed and excreted, thus drainage of alkali and a tendency to acidosis may follow continued use of magnesium sulphate as an aperient. It is given in conjunction with peptone for the so-called medical drainage of the bile ducts, but the action produced is a reflex from the duodenum:

℞	Peptoni	gr. xxx
	Mag. Sulph.	ʒi gr. xv
	Syr. Zingib.	♏xx
	Aq. Menth. Pip.	ad ℥i
	ft. mist.	pro dos.

The best results are obtained when the dose is given upon an empty stomach. An aperient action is obtainable with many patients when a small dose of magnesium sulphate is injected subcutaneously; irritation of the gut during excretion of the salt into it is usually advanced as the explanation of this action. In bacillary dysentery a good effect follows drachm doses of magnesium or sodium sulphate, often combined with dilute sulphuric acid, every two hours. Hypertonic saline, intravenously, may become necessary, however, to equalise the loss of salts and fluid following dehydration. Externally, a 50% solution dabbed on the skin and allowed to dry exerts a mild tonic and astringent action, and is used for cosmetic purposes. Wet dressings of a saturated solution are applied to relieve the pains of arthritis and other local inflammatory conditions, and to stimulate indolent ulcers. The paste of the B.P.C. is used in the treatment of boils and carbuncles; it relieves pain and promotes evacuation of the boil by osmosis. On account of the depressant action of the magnesium ion on the motor cortex, magnesium sulphate is sometimes used parenterally to control convulsions. Tetanus has been treated by intraspinal or subcutaneous injection of 15–75 min. of a 25% solution. In the convulsions of hypertensive encephalopathy and eclampsia the above dosage may be used intraspinally or up to 6 fl. dr. of a 10% solution given intravenously, or intramuscularly as a 20% solution.

Pasta Magnesii Sulphatis, B.P.C. A topical application for boils, etc., containing exsiccated magnesium sulphate phenol and glycerin.

Sodii Phosphas, ½–4 dr. (Di-sodium hydrogen phosphate).

Sodii et Potassii Tartras, 2–4 dr. (Rochelle Salt).

Sodii Sulphas, ½–4 dr. (Glauber Salts).

The three salts above are similar in their aperient action. The phosphate is practically tasteless, hence is especially suitable for children. Rochelle salt is a component of Seidlitz powder (*q.v.*).

Pulvis Effervescens Compositus, Off. (Seidlitz Powder).

Sodii Phosphas Effervescens, B.P.C. 1–4 dr.

Sodii Sulphas Effervescens, B.P.C. 1–4 dr.

Miscellaneous Aperients

Glycerinum, 1–2 fl. dr.

Glycerin taken internally exercises a very slight laxative action; rectally, however, as an injection or in the form of a suppository, it withdraws water from the surrounding tissue and induces rapid and painless evacuation. A large volume of sterile glycerin is instilled into the uterus to drain exudations from the wall in septic conditions. It is a common component of cough linctuses as a demulcent, and it is widely used as a vehicle for other medicaments for application to mucous surfaces. In calamine lotion, and other preparations for external use, a small proportion of glycerin keeps the skin supple, and by leaving a faint film after evaporation of the lotion causes better adhesion of the calamine.

Suppositorium Glycerini, Off.

This suppository contains about 70% of glycerin and provides a convenient method of using glycerin as an aperient. A small-sized glycerin suppository for infants is available commercially.

Sapo (Soap).

The sodium and potassium salts of stearic, oleic and other fatty acids are used under the generic name of " soap " for their detergent properties. In aqueous solution they lower the surface tension of water, thus increasing its cleansing action, and promote the emulsification of fats. Soap enema is used for prompt evacuation of the bowels, but "enema rash," due to the unavoidable alkalinity of the solution, may follow its use.

Enema Saponis, B.P.C.

Sulphur Præcipitatum.

Confectio Sulphuris, B.P.C. 1–2 dr.

Sulphur Sublimatum.

Internally, sulphur is partly converted into sulphide in the intestine; the sulphide mildly irritates the mucous surface of the large intestine, causing soft and painless motions. Externally, sulphur is used as a parasiticide and in chronic skin diseases. In *acne vulgaris* it "peels" the overgrowth of horn cells. A sterile 1% solution in olive oil is injected into the muscle on alternate days with increasing dosage (♏vii–ʒii) to cause a sharp controllable rise in temperature in the treatment of non-specific arthritis, etc., and as an alternative to the malarial treatment of neurosyphilis. This is one form of pyrexia therapy.

Colloidal Sulphur.

Colloidal Sulphur is used externally in scabies, etc., and by mouth or intramuscular injection in rheumatoid arthritis. The minute subdivision of the sulphur particles may enhance their action.

*Contramine.**

Is a complex organic compound containing sulphur, recommended for chronic rheumatism and chronic gonococcal infections. *Thiohistamine,** a sulphur derivative of histamine, has similar uses.

Unguentum Sulphuris, Off. This ointment is used mainly for the treatment of scabies.

Mesulphen (*Sudermo,** *Mitigal**).

This complex organic sulphur compound is applied externally for scabies, etc.

* * * * * *

Amongst other drugs used at times to exert a cathartic action, the following are discussed elsewhere in this volume:

Acetylcholine.
Physostigmine.
Neostigmine.
Posterior Pituitary.
Pilocarpine.
Strychnine.
Ox-bile.

ANTHELMINTICS

ANTHELMINTICS are substances used to promote the expulsion of worms from the alimentary tract. They should be given on a fasting stomach, and their administration should be preceded and followed by brisk purgation, since the parasites are seldom actually killed; the drugs employed usually render them less able to resist peristaltic movement. The terms **Vermifuge,** a substance which causes worms to migrate to the rectum, and **Vermicide,** a substance which kills worms, are sometimes used as synonymous with anthelmintic, but for the reason given above "vermicide" is not really appropriate. Especially in the case of young children suffering from threadworms, the perianal application of Ammoniated Mercury Ointment is advisable, to destroy ova and check irritation, thus minimising risk of subsequent re-infestation from finger-nails.

Aluminii Subacetas, 5–15 gr.

An insoluble powder used against threadworms; the dose is given thrice daily for three days.

Areca (Betel Nut) 15–60 gr.

Powdered areca nut is occasionally used as a tænicide. It may be given in cachets or made into a confection with honey, etc.

Betanaphthol (*q.v.*).

Carbonei Tetrachloridum, ½–1 fl. dr.

Carbon tetrachloride is used against hookworm. It exerts a toxic action on the liver which is similar in character to, but more pronounced than, that of chloroform, and it is, therefore, contraindicated in all cases where pre-existing liver damage may be suspected (*e.g.* in alcoholic subjects). It may cause renal damage. Many patients with hookworm infestation have roundworms and strongyloides associated, and preliminary treatment of these with oil of chenopodium (*q.v.*) is useful to minimise obstruction and irritation of the bowel, which would favour the absorption of carbon tetrachloride. The incidence of toxic effects, including some fatalities, from carbon tetrachloride is sufficiently high to warrant premedication with calcium and dextrose to minimise its action on the liver. See also amino acids.

Diphenan (*Butolan**).

Diphenan, a phenolic derivative, provides effective therapy against threadworms, with low toxicity to the host. It is usually prepared in tablet form each containing 7½ grs. and, for adults, the dose is half to one tablet three times a day for a week. For children, half a tablet, more or less according to age, is given thrice daily for a week. In refractory cases the treatment should be supplemented with enemata containing hexylresorcinol (*q.v.*), quassia or oil of chenopodium. Diphenan may cause some diarrhœa, but otherwise a saline aperient should be given in the mornings during treatment.

Filix (Male Fern rhizome).

Male fern owes its tænicidal properties to a complex compound termed filicic acid. The drug exerts a toxic effect on the tapeworm, which loosens its attachment to the intestinal wall so that it can more easily be swept from the bowel by brisk purgation. The extract is usually administered in capsules and the official Compound Senna Mixture is a suitable aperient. Castor oil should not be used, as it tends to assist absorption of filicic acid, which is highly toxic. Male fern sometimes gives rise to gastro-enteritis. If absorption takes place, convulsions, jaundice, optic neuritis and coma may result. Great caution is needed in prescribing it in marked cases of anæmia or of chronic alcoholism. The following emulsified preparation may be used in dosage proportionate to age when capsules are unacceptable:

℞	Ext. Filicis	ʒi
	Mucil. Acaciæ	ʒi
	Tinct. Senegæ	♏x
	Ext. Glycyrrh. Liq.	ʒſs
	Syr. Zingiberis	ʒſs
	Aq. Menth. Pip.	ad ℥i
	ft. emulsio.	

Extractum Filicis, Off. 45–90 min.

Hexylresorcinol (*q.v.*).

Iodoformum (*q.v.*).

Oleum Chenopodii, 3–15 min.

Oil of chenopodium, or American wormseed, is used to expel roundworm and tapeworm; it has also been used for hookworm, but is inferior to carbon tetrachloride in that respect. The dose is best given divided into three portions at hourly intervals, the final dose being immediately followed by a dose of castor oil or Compound Senna Mixture. The oil is usually administered in soft gelatin capsules, or on sugar for children. The active principle, ascaridole, is sometimes used instead of the parent oil.

Oil of chenopodium must be used with caution in anæmic subjects and cases of cardio-renal disease. Vomiting, vertigo and tinnitus are toxic symptoms. Deafness sometimes lasting for years has also been reported, while convulsions, coma and death have followed gross overdosage.

Oil of chenopodium has proved very successful in enema form against threadworms. Three to ten minims dispersed in a few ounces of water with the aid of a little mucilage of acacia is the dosage recommended for this purpose.

Oleum Terebinthinæ, 3–10 mins. Anthelmintic: 2–4 fl. dr.

Oil of turpentine possesses the general properties of the volatile oils (*q.v.*). Anthelmintic doses against tapeworms and threadworms are best administered with castor oil and may be given by mouth or in the form of an enema. The drug is not now greatly used, however, for its anthelmintic properties. Externally oil of turpentine is applied as a rubefacient, and it forms the basis of various liniments intended to be applied with friction for the relief of sprains, myalgias, etc. Turpentine enema is used to evacuate the bowel and for the relief of flatus. For this, and for anthelmintic purposes, the following, in quantity suitable to age and condition, may be prescribed:

℞	Ol. Terebinth	ʒiv
	Ol. Olivæ	℥i
	Sapo Moll.	ʒiv
	Aq.	ad Oi
	ft. emulsio. pro enema.	

Turpentine is sometimes used for inhalation with steam in bronchitis, etc., but terebene (*q.v.*) is preferable.

Linimentum Terebinthinæ, Off.

An embrocation to be applied with friction to promote local hyperæmia.

Pelletierinæ Tannas, 2–8 gr.

Pelletierine tannate, a mixture of the tannates of alkaloids from pomegranate root-bark, is an effective tænicide. It is administered as a powder or tablet on an empty stomach and followed, after two hours, by full dosage of castor oil.

Compound Senna Mixture is given later if the castor oil fails to take effect. The drug is dangerous to children and to debilitated patients, in whom it may give rise to toxic sequelæ similar in type to those produced by male fern.

Quassia.

A strong infusion of quassia, to which may be added 5% of sodium chloride, is often injected rectally to expel threadworms. The treatment is especially suitable for infants to whom anthelmintic drugs orally may be dangerous, but in any case a rectal injection containing hexylresorcinol or oil of chenopodium is much more efficacious. The injection should be of small bulk so that it may more easily be retained for a short time.

Santoninum, 1–3 gr.

Santonin is a white, crystalline principle obtained from various species of wormseed (*Santonica*). It is insoluble in water and is best given in powder or tablet form. When exposed to light it turns yellow, forming what is called "photosantonin," and, formerly, it was not uncommon to prescribe this coloured substance in the empirical belief that its anthelmintic activity was higher. Santonin is used against roundworms and threadworms; it causes the parasites to migrate to the rectum, whence they can be expelled by a brisk evacuant, or the use of a suitable enema solution. The drug may produce gastroenteritis, and its absorption is liable to give rise to xanthopsia, convulsions and liver damage. Castor oil assists its absorption and is, therefore, contraindicated as the accompanying purgative. It should not be used for infants under two years of age and the dosage thereafter is ⅛ gr. per year of age. A very small preliminary dose is advisable to test for idiosyncrasy. Calomel, magnesium sulphate or Compound Jalap Powder are suitable aperients to use with santonin.

For a child of three years:

℞	Santonin	gr. ſs
	Calomel	gr. ſs
	Pulv. Jalap. Co. Sucrosi }	āā gr. v
	ft. pulvis. pro dos.	

Thymol (*q.v.*).

Thymol is used occasionally for adult patients in the treatment of roundworms. The usual dose is 60 gr. in two divided doses, the drug being finely powdered and admixed with an equal weight of lactose to prevent its aggregation. Its use should be preceded and followed by Compound Senna Mixture to keep the bowels freely opened. Toxic effects from thymol are rare, but nausea, vomiting, giddiness and collapse have been reported.

Viola Crystallina (*q.v.*) (*Medicinal* Gentian Violet).

The anthelmintic properties of crystal violet are described under the main monograph dealing with the drug which appears in the chapter on **Antiseptics.** Crystal violet is often referred to as gentian violet, but commercial gentian violet is an impure mixture which should not be used medicinally.

ASTRINGENTS

The astringents comprise all substances which, applied locally, check the discharge from and/or shrink a tissue. The term is also applied to styptics or hæmostatics, and these are further divided into direct and remote. The former check hæmorrhage when applied locally, the latter increase the coagulability of the blood. Lastly, drugs administered internally to check diarrhœa are also included. Most astringents are fully considered under other sections, which should be consulted; for facility of reference, however, they are tabulated here. *A description of those not discussed elsewhere follows the table.*

MODE OF ACTION	*SUBSTANCE*
Withdrawal of water	Alcohol (95–100%).
	Glycerin.
Physical Absorbents	Bismuth Carbonate.
	Bismuth Subgallate.
	Calcium Carbonate.
	Kaolin.
Precipitation of Protein	Methyl Violet.
	Many soluble salts, especially of the heavy metals.
	Sulphuric Acid.
	Tannic Acid.
Vaso-constriction	Adrenaline applied locally.
Increased Coagulability of blood	Congo red.
	Soluble Salts of Calcium.
	Sodium citrate solution (parenterally).
	Theophylline with Ethylenediamine.
	Tissue and blood preparations.
	Alginates.
	Viper venom.
	Vitamin K (in cases of its deficiency).

Acidum Tannicum, 5–10 gr.

Tannic acid applied to a mucous or an abraded surface reacts with protein to form an insoluble compound; it is, therefore, strongly astringent, and is used both internally and externally for this purpose but is inclined to give rise to irritation. For internal use preparations of catechu, kino, etc., are better tolerated. In the mouth a 20% alcoholic solution is applied to spongy gums. A 2% aqueous solution is suitable as an astringent mouth wash, for packing the nose to control epistaxis and for application to mucous surfaces generally. A freshly prepared 2% aqueous solution has been largely used in the treatment of burns and scalds, but should never be employed near the eyes or the fingers or toes, as contracture of the lids and gangrene of the extremities may occur as a result of the powerful coagulant action. There is evidence, too, of liver necrosis following the use of tannic acid to extensive burns. The official suppository and ointment are used against inflamed hæmorrhoids.

Glycerinum Acidi Tannici, Off. 10–30 min.

Suppositorium Acidi Tannici, Off.
Each suppository contains 3 grains of tannic acid.

Trochiscus Acidi Tannici, Off.
Each lozenge contains ½ grain of tannic acid.

Unguentum Acidi Tannici, B.P.C.

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The following commonly used drugs owe their properties to the presence of one form or another of tannic acid; their preparations are less irritant to the stomach than tannic acid itself:

Catechu (a plant extract).
Hamamelis (bark and leaves).
Kino (dry juice from a tree).
Krameria (rhatany root).

Tinctura Catechu, Off. ½–1 fl. dr.
This tincture, which also contains cinnamon as a carminative, is usually used in conjunction with chalk and opium for diarrhœa.

Extractum Hamamelidis Liquidum, ½–1 fl. dr.
5% in water forms a useful astringent bladder wash and rectal wash-out in ulcerative colitis.

Liquor Hamamelidis, B.P.C. (*Pond's Extract,** sim.).
The astringent properties of this preparation, which is distilled from the fresh leaves, are very slight. It is used in evaporating lotions.

Pulvis Kino Compositus, B.P.C., 5–20 gr.
Powdered kino with opium (5%) and cinnamon.

Extractum Krameriæ Siccum, Off. 5–15 gr.

Tinctura Krameriæ, B.P.C. ½–1 fl. dr.

Trochiscus Krameriæ, Off.
Krameria lozenges are used for relaxed sore throats.

Trochiscus Krameriæ et Cocainæ, Off.
Each lozenge contains $\frac{1}{20}$ gr. of cocaine hydrochloride with dry extract of krameria.

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Acetannin, B.P.C. (*Tannigen**),5–10 gr.

Albuminum Tannicum (*Tannalbin**), 8–15 gr.
These preparations pass through the stomach unchanged but are soluble in the intestine, where they exert the astringent action of tannic acid. They are employed to check diarrhœa and in ulcerative colitis.

Congo Red (an azo dyestuff).
Congo red is injected intravenously in a dosage of 0·25 ml. of 1% solution per kilo. bodyweight. It produces an increase in monocytes, blood platelets and fibrin content, and is used mainly to control hæmoptysis. A slight rigor may follow its injection. By means of a special technique, Congo red is used in the diagnosis of amyloid disease as its special affinity for amyloid tissues causes its rapid disappearance from the blood.

Tissue Preparations.

A number of substances are employed to reduce the clotting time of blood and so check hæmorrhage. Of these may be mentioned *Coagulen-Ciba,** derived from normal bovine blood platelets; this is supplied in powder form for local use, and in ampoules for injection. *Thromboplastin** is a sterile suspension of comminuted brain tissue for local application. Hæmostatic serum (*Hemoplastin,** sim.) contains in solution prothrombin and thrombokinase derived chiefly from the blood of horses and cattle. A recent and effective development has been the employment of *fibrinogen* with added *thrombin* to form *fibrin foam or films* for the arrest of bleeding. It is also used as a fixative in plastic surgery. It is absorbable and does not inactivate penicillin, but cannot be heat-sterilised. Thrombin solution (1,000 Iowa units per mil.) or powder is a useful hæmostatic. Other effective absorbable hæmostatics for local application are *oxidised cellulose* (oxycellulose) and the *gelatin sponge* of whipped or foam gelatin. The former inactivates penicillin, cannot be heat-sterilised and is best used without thrombin, the latter does not inactivate penicillin, can be heat-sterilised and can be used with thrombin. *Alginic acid* and its salts, *sodium* and *calcium alginate*, are effective styptics for application to oozing surfaces, and are derived from sea-weed. They resemble cellulose in chemical structure. Alginic acid and sodium alginate, when applied to a bleeding surface, react with calcium ions to form a calcium alginate clot. Calcium alginate by releasing calcium may also aid prothrombin formation. These substances can be sterilised by heat and calcium alginate is absorbable and not harmful to the tissues.

Viper Venom.

Preparations of the venom of Russell's viper such as *Stypven** have a powerful hæmostatic action when applied topically. Hæmorrhage from hæmophilics has been controlled with the solution, and it is of great value in dental hæmorrhage.

Moccasin venom is said to be of value in cases of purpura and other bleeding when injected subcutaneously in dosage of 0·2 to 1 ml. of a 1 in 3000 solution. It is not used in hæmophilia.

ANTICOAGULANTS

Heparinum.

Heparin is an anticoagulant substance prepared from liver or ox lung; it is possibly identical with antithrombin, normally present in blood. It is a mucoitin polysulphural ester and is standardised so that one international (or Toronto) unit is equivalent to 0·01 mg. of pure heparin serum salt. It is usually made up as a solution so that 1 ml. contains 1000 i.u. (10 mg.). Heparin is the most powerful anticoagulant known and it is used in the prevention and treatment of post-operative thrombosis and in the treatment of coronary and other types of thrombosis, also in vascular surgery. In these conditions it is generally administered in the first 48 hours of treatment, when it is given concurrently with dicoumarol (see below) because the action of the latter is delayed. After this period, treatment can be continued with dicoumarin alone. Heparin dosage is adjusted so that the clotting time is maintained between 15 to 30 minutes. The drug is administered intravenously either as a continuous drip (1000–2000 i.u. per 100 ml. of normal saline per hour) or 5000 i.u. 4-hourly during the day, the last dose being increased to 10,000 i.u. The drug should be avoided where there is a hæmorrhagic tendency. It has also been used to prevent the clotting of blood removed for transfusion by adding 1 i.u. heparin to each ml. of blood withdrawn. (See also below.)

Dicoumarol, Off. (Dicoumarinol, *Temparin**).

This substance, which was first isolated from spoiled, "sweet-clover" hay, has subsequently been synthesised. Its chemical name is 3“3” methylene-bis-(4 hydroxycoumarin). When administered by mouth, dicoumarol diminishes the prothrombin content of the blood by reducing its formation in the liver, a drop in the prothrombin index occurring. In consequence, the blood becomes less coagualable, and dicoumarol, like heparin, has been used to diminish clotting and thus prevent post-operative thrombophlebitis (particularly in the obese after pelvic operations and in the presence of varicose veins) and embolism. It is employed in vascular surgery and recently in coronary thrombosis. Dicoumarol has no action *in vitro*.

Comparison of Actions of Dicoumarol and Heparin

Dicoumarol	**Heparin**
Acts by diminishing prothrombin.	Inhibits thrombin formation.
Effective by mouth.	Only effective by intravenous injection.
Action delayed in onset (2–3 days) but prolonged in effect (1–2 weeks).	Action rapid but transient.

Dicoumarol is therefore useful for prolonging the brief effects of heparin (see above). In general, it is non-toxic but, like heparin, it can give rise to hæmorrhage, particularly from operation sites and alimentary and renal tracts. A daily determination of the prothrombin level of the blood is desirable during its administration. Contraindications to its use are hæmorrhagic diseases, widespread embolism, liver disease and renal insufficiency. It should also not be given where bleeding is to be anticipated after labour or operation. If bleeding occurs, menaphthone (vitamin K) injections and blood transfusions may be necessary, as well as ascorbic acid and nicotinamide.

Dosage: Dicoumarol is usually administered in capsules in doses of 200–300 mg. daily. A maintenance dose of 50–200 mg. daily or less frequently is required to keep the prothrombin concentration to 10 to 20% of its normal level. A di-sodium dicoumarin is available for parenteral administration in 100 mg. ampoules.

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The dicoumarol molecule can be quantitatively degraded into salicylic acid, and it has been shown that salicylates lower the prothrombin level of the blood and occasionally cause bleeding, especially into the subcutaneous tissues. These hæmorrhages can be prevented but not cured by vitamin K. It is suggested that the latter should be concurrently administered when large doses of salicylates are used.

EXPECTORANTS AND EMETICS

Expectorants are medicinal agents which increase the output of bronchial secretion. There is clinical and experimental evidence that these substances are of value in relieving the dry, inflamed bronchial membrane in acute bronchitis. On the other hand, recent work suggests that, quite contrary to what has been accepted in the past, expectorants are of little benefit in chronic bronchitis and bronchiectasis. Some expectorants may act by being excreted by the bronchial mucosa, *e.g.* potassium iodide and guaiacol; the action of others is by irritating the vagal nerve-ends in the stomach, thus exciting the cough reflex and bronchial secretion. Drugs belonging to this latter group are often referred to as **stimulating expectorants**; examples are ipecacuanha and ammonium carbonate. In large doses the reflex irritation produced involves the vomiting centre and these drugs act as **emetics.**

It should be noted that increased bronchial secretion not only relieves a dry, acutely inflamed membrane, so reducing the irritant cough, but makes the bronchial secretion less viscid and so facilitates its expulsion. The following expectorants act, following their excretion by the bronchial mucosa:

Acidum Benzoicum, 5–15 gr.

Taken by mouth, benzoic acid and the alkali benzoates appear in the bronchial and salivary secretions and exert a feebly antiseptic as well as an expectorant action. The acid itself is a gastric irritant and is rarely used except as a component of paregoric (*q.v.*). Ammonium or sodium benzoate are preferable and are sometimes used in bronchiectasis. The benzoates exert a mild antiseptic action in the urine and were formerly employed for this purpose. They are excreted as salts of hippuric acid.

Alkalis (*q.v.*).

Since alkali has a solvent action on mucus, any shift in reaction of the secretion towards increased alkalinity loosens phlegm. "Hot-water" mixtures of the following type are well regarded by clinicians for loosening tenacious bronchial mucus, and relieving the severe paroxysms of cough associated with chronic bronchitis:

℞	Sodii Chloridi	.. ..	gr. iii
	Sodii Bicarb.	.. ..	gr. x
	Aq. Anisi	.. ..	ad ℥ſs
	ft. mist.	pro dos.	

The dose should be sipped slowly in a tumblerful of very hot water.

Ammonii Chloridum, 5–60 gr.

This is excreted by the bronchial glands and exercises a solvent action on mucus; it also excites the ciliated epithelium to increased activity. The salt is fully discussed in the chapter on salt action.

Creosotum (*q.v.*).

Iodides (*q.v.*).

Terpini Hydras, 3–10 gr.

Terpene hydrate resembles creosote in action but it is less irritant to the stomach. Combined with diamorphine it is sometimes used to relieve severe cough in phthisis.

Terebenum, 5–15 min.

Terebene acts like the volatile oils. It is an aromatic substance prepared from oil of turpentine, and is a common ingredient of antiseptic pastilles.

Volatile Oils (*q.v.*).

Stimulating Expectorants

Acidum Aceticum Dilutum, Off. (*q.v.*).

Ammonii Bicarbonas, 5–10 gr.

Ammonii Carbonas, 5–10 gr.

The mode of action of these and other stimulating expectorants has been briefly indicated in the introduction to this chapter. These salts are converted into ammonium chloride in the stomach. Inhaled as "smelling salts," the ammoniacal fumes of ammonium carbonate are used as a reflexly acting restorative in faintness, etc.

Spiritus Ammonii Aromaticus (Spirit of Sal Volatile), Off. 15–60 min.

This is given diluted with water as an expectorant and also a reflex medullary stimulant in fainting.

Apomorphinæ Hydrochloridum

Dosage: Expectorant: $\frac{1}{64}$–$\frac{1}{32}$ gr.
Hypnotic and emetic: $\frac{1}{32}$–$\frac{1}{8}$ gr.

Injected subcutaneously, apomorphine hydrochloride may produce rapid emesis by direct stimulation of the centre; in smaller doses it is an expectorant. A dose of $\frac{1}{40}$ gr. dissolved in 1 drachm of aniseed water and administered orally every three hours is a reliable expectorant, especially valuable in cases where irritants of the gastric mucosa are contraindicated. It is occasionally used in alcoholic delirium to empty the stomach and later produce sleep, but in cases of narcotic poisoning it is unreliable owing to previous depression of the vomiting centre produced by the narcotic. In any event, evacuation of the stomach by means of a tube is now considered preferable to the use of emetics. In cases of corrosive poisoning, of course, neither the stomach tube nor emetics are safe to employ.

Ipecacuanha.

This Brazilian root owes its properties chiefly to the alkaloids emetine and cephaëline. Given by mouth it is a slow-acting but reliable emetic which is given in croup, since the violent expiratory movements produced by vomiting and stimulation of the cough centre aid in the expulsion of secretions. In larger doses irritation of the gastric mucosa may spread to the intestine and cause diarrhœa. Like all substances which stimulate the vomiting and secretory centres, it causes increased perspiration and is used, combined with opium as Dover's Powder, for its sudorific properties in broncho-pneumonia, influenza, etc. Some suitable expectorant prescriptions containing ipecacuanha are:

℞	Ammon. Bicarb.	gr. x
	Tinct. Ipecac.	♏xv
	Syr. Tolu.	ʒſs
	Aq. Anisi	ad ℥ſs
	m. ft. mist.	pro dos.

℞	Pot. Iodid.	gr. x
	Pot. Acetat.	gr. xx
	Tr. Scillæ	♏x
	Ext. Glycyrrh. Liq.	ʒſs
	Spt. Chlorof.	♏x
	Aq. Anisi	ad ℥ſs
	m. ft. mist.	pro dos.

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Emetine.

The alkaloid **emetine** exerts a specific destructive action on Entamœba histolytica. Owing to its irritant effect on the gastric mucosa, adequate dosage by mouth can only be achieved by administering emetine bismuth iodide in capsules. This salt passes through the stomach largely unchanged, but yields emetine by slow hydrolysis in the intestine. The emetine is absorbed and, reaching the liver by way of the portal circulation, it can deal with any of the parasites which may have become encysted in that organ. The concurrent intramuscular administration of emetine hydrochloride is desirable, as most of the emetine so given is excreted into the large intestine and can destroy parasites in the walls and the lumen of the gut. A little may appear in the gastric secretion and give rise to nausea. Despite its toxic action on the heart in experimental animals, it is safe in therapeutic doses if the patient is kept in bed.

Emetine Hydrochloridum, ½–1 gr. by parenteral injection daily for 6 to 10 doses.

Emetine Bismuthi Iodidum, 1–3 gr. by mouth.

This drug is administered for 14 days, and as it may cause vomiting and diarrhœa, each dose is given at about 10 p.m. and is preceded by a sedative such as phenobarbitone.

Ipecacuanha Pulverata, Off. ½–2 gr.; *emetic* 5–15 gr.

Pulvis Ipecacuanhæ et Opii (Dover's Powder), Off. 5–10 gr.

Tinctura Ipecacuanhæ, 10–30 min; *emetic* ½–1 fl. oz.

Digitalis, Scilla.

Both of these drugs, particularly squill, cause gastric irritation and so promote expectoration. The chief benefit of digitalis resides, however, in the improved general circulation which follows its administration in suitable cases, and this is discussed under the main actions of the drug.

Quillaia (a bark), Senega (a root).

These drugs contain glycosides, called saponins, which lower the surface tension of water. An aqueous solution containing saponin froths like a solution of soap and it has considerable detergent properties. Saponins are used to emulsify preparations chiefly for external use, and in the composition of soapless shampoos. Administered internally they irritate the stomach, and liquid preparations of senega are largely employed as expectorants.

℞	Potass. Acetat.	gr. xxx
	Amm. Carb.	gr. v
	Tinct. Ipecac.	♏x
	Spt. Anisi	♏x
	Infus. Senegæ	ad ℥ſs
	ft. mist.	pro dos.

Tinctura Quillaiæ, Off. ½–1 fl. dr.

Infusum Senegæ, Off. ½–1 fl. oz.

Extractum Senegæ Liquidum, Off. 5–15 min.

Sodii Chloridum.

Common salt in the proportion of one tablespoonful to half a tumbler of warm water is an efficient domestic emetic. The more orthodox medicinal uses of sodium chloride are discussed elsewhere.

Drugs depressing the Cough Centre

Mixtures containing morphine, diamorphine or codeine are used, especially at night, to check cough temporarily and so permit of sleep to the patient. Such therapy can be coupled with more active expectorant treatment for use during the daytime, or may be employed in the case of patients who need relief from the strain of a harassing cough. The following preparations are of a general type:

℞	Syr. Codein.	
	Syr. Tolu.	
	Tinct. Opii Camph.	p. æq.
	ft. linctus.	ʒi pro dos.

℞	Terpin Hyd.	gr. v
	Codein Phosph.	gr. ½
	Menthol	gr. ¼
	ft. oblatum.	

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The inhalation of medicated steam is one of the most useful ways of obtaining relief from the cough of tracheitis, etc. Various volatile oils and Friar's Balsam (*q.v.*) are commonly employed to provide the medication.

RESPIRATORY, VASOMOTOR AND CIRCULATORY STIMULANTS

THE two most vital centres of the medulla, namely the respiratory and vasomotor, can be affected by substances in the blood acting directly upon these centres, or reflexly by a peripheral afferent stimulus such as is produced by slapping or "plucking" an unconscious patient, by inhalation of ammonia or by swallowing a gastric irritant such as Aromatic Spirit of Ammonia (*q.v.*). Many of the drugs described in this chapter act upon both of the centres mentioned, but the action may be much more marked upon one of them. Nikethamide, for example, acts chiefly on the respiratory centre and adrenaline upon the vasomotor centre.

These centres can function properly only in the presence of adequate oxygen and carbon dioxide tension in the blood. In the condition of medullary depression by drugs, anæsthetics, carbon monoxide poisoning, drowning and asphyxia of the new-born, the inhalation of oxygen with 7% of carbon dioxide causes stimulation of the medulla. In fact, carbon dioxide is the most powerful respiratory stimulant. Furthermore, anoxia is an important factor in the production of medullary depression in the above states, and medullary depression, in itself, aggravates anoxia. Thus a vicious circle is set up, and the value of oxygen therapy for medullary depression becomes obvious. The use of peripheral stimulation, as mentioned above, may assist in cases of temporary medullary depression, *e.g.* fainting attack, but should be avoided where there is marked and prolonged circulatory collapse in such states as traumatic shock, severe degrees of asphyxia of the new-born, etc. It is important to emphasise that in such conditions of anoxia, a drug stimulating the respiratory centre will, by relieving anoxæmia and supplying the brain with more adequately oxygenated blood, help to stimulate the vasomotor centre and improve the circulation.

Adrenalina (and other sympathomimetic drugs) (*q.v.*).

Atropinæ Sulphas (*q.v.*).

Caffeina, 2–5 gr.

Caffeine is an alkaloid derived from tea and coffee. Administered by mouth its main action is to produce diuresis (*vide* purine bases). When administered by subcutaneous injection, soluble compounds of caffeine first stimulate the sensory area of the brain. Fatigue is diminished, the special senses become more acute and association is improved. Unlike that produced by cocaine, the stimulation is not followed by depression. The respiratory centre is directly stimulated together with the medulla generally, and this action is of therapeutic importance in the treatment of medullary depression following narcotic poisoning. The only important direct action of caffeine on the heart is to improve the blood supply by dilatation of the coronary arteries, indirectly it is of use in case of heart disease by promoting diuresis, but it is inferior to theobromine and theophylline. In large doses it increases the heart rate by stimulating the pacemaker, toxic doses depress cardiac muscle. Caffeine is used to relieve fatigue, and some cases of migraine[1] and congestive headache are benefited. It is occasionally used for the relief of bronchial asthma by relaxing the bronchial muscle spasm. It causes increased gastric secretion.

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[1] It may help to abolish cerebral vasospasm present in the early stages of migraine.

Caffeina et Sodii Benzoas, 5–15 gr.; by injection, 2–5 gr.

Caffeina et Sodii Salicylas, 5–15 gr.; by injection, 2–5 gr.

Both of the above water-soluble compounds of caffeine are stable in solution and suitable for oral or parenteral use.

Tabella Acidi Acetylsalicylici Compositæ, B.P.C. ("**A.P.C.**").

These tablets contain aspirin phenacetin and caffeine and are used against headache, myalgias, etc. Dose: one or two tablets.

Camphora (*q.v.*).

Carbonei Dioxidum.

The physiological importance of carbon dioxide in regard to the medullary centres has been touched upon in the introduction to this chapter. Inhalation of the gas increases the rate and depth of the respiratory excursion, and clinically it is used to stimulate a depressed respiratory centre and to increase the volume of respiration in order to hasten the excretion of gases or vapour (coal-gas, ether vapour, etc.). For these purposes it is usual to employ a mixture of oxygen containing 7% of carbon dioxide. If the respiratory centre is greatly depressed, as by narcotics, it may be necessary to resensitise it with the aid of strychnine or a similarly acting drug before normal response to carbon dioxide can be obtained. The brief inhalation of pure carbon dioxide will often terminate an attack of hiccough.

Carbon dioxide "pencil" obtained by allowing the compressed gas to escape into a washleather bag and moulding the resulting "snow" into shape is used locally as a cautery. It destroys tissue by extreme cold, and is employed to remove warts, birthmarks, etc.

Digitalis, etc. (*q.v.*).

Leptazolum, Off. ¾–1½ gr.

Leptazol is the official name for pentamethylene tetrazole, which is also known as *Cardiazol.** This compound exerts a strong stimulant action on the respiratory centre and, to some extent, on the vasomotor centre. It is used in small doses to assist resuscitation in cases of respiratory failure in drowning, during anæsthesia, by the action of depressant drugs, or in pneumonia. Leptazol has little, if any, direct action on the heart, but the raised blood-pressure and circulatory improvement which follow vasomotor stimulation lead to an increased blood supply to the coronary arteries, and it is therefore of value in acute collapse. Leptazol is active if administered either orally or rectally, but where a prompt response is needed it can be given by intramuscular or intravenous injection. Large doses intravenously produce clonic convulsions, similar to those produced by other analeptic drugs exerting a camphor-like action on the motor cortex. This effect has been utilised as a shock therapy in the treatment of schizophrenia and depressive neuroses, but electrical methods of producing shock, which can be regulated with more certainty, are now preferred if available.

Injectio Leptazoli, Off. 8–15 min. by subcutaneous injection; 30–75 min. increasing to 180 min. by intravenous injection as a convulsant.

Hexazole (*Azozole**).

This is a similar drug to leptazol and is used as an aqueous 5% solution in doses of 0·5 to 2·5 mil., given intramuscularly or intravenously in the convulsion therapy of schizophrenia. It is said to have less unpleasant effects in this type of treatment than leptazol.

Lobelinæ Hydrochloridum, $\frac{1}{27}$–$\frac{1}{7}$ gr.

Lobeline is the principal alkaloid of lobelia herb. It exerts a selective and powerful stimulating action of short duration on the respiratory centre, and the hydrochloride is injected parenterally to stimulate the respiration of new-born infants, in partial suffocation (drowning, etc.), overdosage of narcotic drugs, and in other conditions where there is respiratory failure. The injection may be repeated several times at fifteen-minute intervals.

Preparations of lobelia are sometimes used as antispasmodics in bronchial asthma but the action is variable. Stimulation followed by depression of the ganglia of the autonomic nervous system is said to be produced. In this respect lobeline resembles nicotine. Bronchial dilatation is produced by stimulation of the sympathetic ganglia. Compound powders containing lobelia are ignited and the fumes inhaled for the relief of asthmatical paroxysms, *but the inhalation of these irritant fumes tends ultimately to exacerbate the disorder by causing bronchitis.*

Tinctura Lobelia Ætherea, Off. 5–15 min.

Ethereal tincture of lobelia is used in mixtures for the symptomatic relief of bronchial asthma.

Pulvis Lobeliæ Compositus, B.P.C. (Compound Asthma Powder).

This is ignited and the fumes inhaled as described above.

Nikethamidum, Off. 3–8 gr.; 8–20 gr. intravenously.

Nikethamide is the diethylamide of nicotinic acid. In the form of an injection it is known, also, as *Coramine.** When injected, nikethamide exerts, and is used for, a rapid stimulatory effect on the medullary centres similar to that of leptazol (*q.v.*). In the higher range of dosage it is very efficacious intravenously in the treatment of narcotic poisoning such as by barbiturates, and to accelerate rate of recovery after barbiturate and other anæsthetics, or in acute alcoholic stupor. Maximal doses are convulsant. When promptness of action is not essential, nikethamide may be given by mouth.

Injectio Nikethamidi, Off. 35–60 min. intramuscularly; 1¼–4 fl. dr. intravenously.

Other stimulants of this type are *Cycliton,** *Icoral,** *Cardotone** (sodium camphor sulphonate).

Oxygenium.

In the average area, atmospheric oxygen is sufficient to effect a 95% saturation of arterial blood, which expressed quantitatively amounts to 19 mils of oxygen per 100 mils of blood. Of the 19 mils most is combined with hæmoglobin, only about 0·3 mil being in solution at a tension approximately equivalent to 100 mm. of mercury; oxygen being delivered to the tissues at this tension. The effect of breathing high concentrations of oxygen is to complete the saturation of arterial blood to 20 mils per 100, and the increase is mainly in the amount dissolved in the plasma. The greatly increased tension results in more oxygen being delivered to the tissues. This is of prime therapeutic importance when the organism suffers from oxygen-lack (anoxia), with all the serious symptoms consequent on this state. Four types of anoxia are recognised, and oxygen therapy is particularly useful in the first of these, and of value, also, in Types II and III.

Type I (Anoxic type).—This is characterised by a diminished tension of oxygen in the arterial blood and reduced hæmoglobin saturation. It occurs physiologically at high altitudes, and clinically in asphyxia, narcotic poisoning, anæsthesia from volatile anæsthetics, and in lung diseases interfering with the absorption of oxygen from the alveolar air. These include pneumonia, severe pulmonary irritation as from war-gases, emphysema, lung collapse and œdema and pulmonary congestion due to cardiac insufficiency. The type includes, also, congenital heart disease where arterial blood is shunted from the right to the left side without passing through the lungs.

Type II (Anæmic type).—In this type the quantity of functioning hæmoglobin is reduced although the oxygen tension of the arterial blood is normal. The condition may be of anæmic origin or due to the hæmoglobin becoming abnormally combined, for example in carbon monoxide poisoning and methæmoglobinæmia due to drugs, etc.

Type III (Stagnant type).—This is met in cases of circulatory failure, hæmorrhage and traumatic shock, which result in arterial blood being supplied to the tissues in inadequate amounts. The effect of oxygen administration in these cases is to increase above normal its tension in the arterial blood and, in this way, to compensate for the deficient quantity of blood reaching the tissues.

Type IV (Histotoxic type).—Here the tissue cells are poisoned (*e.g.* by cyanide or narcotics) and are unable properly to utilise the oxygen supplied to them.

Oxygen therapy is also of value in the treatment of intestinal distension, gas gangrene and after ventriculograms. The gaseous distension in these states is due mainly to nitrogen. Oxygen acts by displacing nitrogen from the blood, the nitrogen being exhaled by the lungs. This allows more nitrogen to pass into the blood from the distended tissues, thus relieving their distension.

In the United States, where helium is available, a helium oxygen mixture containing 20% by volume of oxygen is administered with great benefit in obstructive diseases of the respiratory tract, including traumatic œdema of the larynx and *status asthmaticus.* The benefit arises because of the high rate of diffusion which the low vapour density of helium confers upon the mixture.

In order to obtain any considerable benefit from oxygen therapy the gas should be delivered to the patient at a concentration of at least 50% (the helium-oxygen mixture is, of course, an exception), and administration should be commenced early before severe anoxia has produced profound, irreversible changes in the tissues, particularly the brain and heart. As dry oxygen is a lung irritant the gas should be bubbled through warm water before reaching the patient. Modern methods of oxygen administration include the tent and the B.L.B. or other suitable mask, which enable a flow of 5 to 8 litres a minute to result in an oxygen concentration of 50–80%. Since above 70% oxygen is a possible lung irritant it should be employed only intermittently at the high levels. For continuous administration a level below 70% should be used. Older methods of giving oxygen by means of a funnel or catheter do not deliver it at sufficiently high concentrations and are unsuitable for severe anoxia. The funnel method in particular is wasteful and should not be employed except in emergency. Oxygen poisoning can also occur from breathing compressed air, *e.g.* in divers, with neurological manifestations such as tingling, nausea, vertigo, depression, hallucinations, twitchings, convulsions and syncope.

Oxygen has been administered by rectal and parenteral injection in a variety of conditions, but although formerly some high claims have been made concerning the efficacy of these procedures, it appears now to be generally agreed that the results are disappointing.

Cytochrome.

Tissue respiration is effected by the cytochrome system. Hydrogen transported from the metabolites and foodstuffs reduces cytochrome, which is then reoxidised by cytochrome oxidase which can react directly with oxygen from the air. Cytochrome C is a conjugated protein containing an iron porphyrin group. It is non-antigenic and non-toxic on injection. It can be prepared from ox-heart. Intravenous injections of 50 to 350 mg. in certain cases of anoxia are followed by its removal from the blood stream to the tissues with improvement in the anoxic state as the result of improved tissue respiration. Further trials are being carried out.

Picrotoxinum, $\frac{1}{100}$–$\frac{1}{25}$ gr.

Picrotoxin is a white crystalline principle obtained from Levant berries, an Oriental fruit. It is a powerful convulsive poison and medullary stimulant, and its principal use is to stimulate the respiratory centre, especially in cases of poisoning by any of the barbiturate group of drugs. For this purpose as much as 100 mg. dissolved in a pint of sterile saline may be administered by drip infusion over a 12-hour period, or in very severe cases at the rate of 1 mg. per minute. Alternatively, 5 mg. intravenously or intramuscularly may be administered every 15 minutes or when the patient lapses into unconsciousness. If twitching occurs and the corneal and pupillary reflexes return, it is an indication that the toxic action of the barbiturate has been effectively neutralised. Severe convulsion can be immediately controlled by minimal dosage of a short-acting barbiturate, such as soluble pentobarbitone, intravenously.

Strychninæ Hydrochloridum, $\frac{1}{32}$–$\frac{1}{8}$ gr.

Strychnine is the principal alkaloid of nux vomica seeds. When a soluble salt such as the hydrochloride is injected in small doses, or slightly larger doses are given by mouth, it augments the motor components (or agonists) of the reflex response and diminishes the inhibitor components (or antagonists). In toxic doses it gives rise to spinal tonic convulsions, abolishing the inhibitor component altogether and changing it into a motor one. As the extensor muscles of the trunk are more powerful than the flexors, although both components contract, the attitude during spasm is one of extension (opisthotonus). Decreased synaptical resistance to afferent stimuli is the cause of these phenomena and it leads to a rapid and widespread irradiation of impulses stimulating motor neurons. In toxic doses respiration is arrested during the convulsion by spasm of the respiratory muscles and death may occur from asphyxia. Consciousness is not lost during the attack of convulsion, and the heart rate is accelerated. In therapeutic doses, however, the rate may be slowed by vagal stimulation. The indications for strychnine therapy are:

1. It is injected as a respiratory centre stimulant in cases of pneumonia and narcotic poisoning. In these cases by relieving anoxæmia it also improves the state of the vasomotor centre and heart muscle; the action being due to the provision of better oxygenated blood to these tissues. It helps to provoke coughing in cases where medullary depression with a feeble cough reflex is accompanied by much pulmonary secretion.

2. In paralytic states, strychnine will sometimes assist in restoration of function provided that there is no complete severance of nerve pathways and no active inflammatory nervous lesions. It helps to prevent atrophy of muscles in such cases.

3. The so-called "tonic" effect of strychnine is mainly derived from its bitterness, when taken by mouth, evoking the Pavlov reflex and improving appetite. In such cases preparations of nux vomica are frequently employed. After absorption of the alkaloid from the small intestine its action on the cord may improve muscle tone and nutrition. The drug has little or no direct action on the brain above the medullary level, but it increases the cerebral blood supply possibly by stimulation of the vagal nuclei and this may assist in its tonic action. Strychnine is used to lessen depression during withdrawal treatment of alcoholism and drug addiction. It is used to improve vision in amaurosis.

Strychnine poisoning should be treated by chloral hydrate rectally, and the intravenous injection of any soluble barbiturate. When the drug has been taken by mouth, tannic acid or potassium permanganate may be given and the stomach washed out under chloroform anæsthesia. Artificial respiration and oxygen with 7% of carbon dioxide may also be necessary.

Liquor Strychninæ Hydrochloride, Off. 3–12 min.

A convenient, stable solution for use in mixtures.

Extractum Nucis Vomicæ Siccum, Off. ¼–1 gr.

This is often added to aperient pills containing anthracene purgatives, as it is thought that strychnine may synergise the aperient effect by augmenting the short reflexes.

Tinctura Nucis Vomicæ, Off. 10–30 min.

This is frequently used as an ingredient of bitter " tonic " mixtures.

MYOTROPIC DRUGS

MYOTROPIC (or musculotropic) drugs are those which exert a direct action on muscle fibre. They are somewhat heterogeneous in origin, and a number of drugs which properly belong to the group, such as acetylcholine and the anthracene purgatives, are more conveniently considered under other headings. They may be classed as positive myotropes, viz. those improving muscle tone, and negative myotropes, *i.e.* those decreasing the tone of the muscle. Negative myotropes are used to abolish muscle spasm, *e.g.* of the coronary arteries in angina pectoris and of the bronchioles in asthma. As the nervous sensitivity of the patient in these states is often a factor in aggravating or precipitating the symptoms, the removal of this nervous factor may be almost as important as the drug used in the prevention of further attacks. This probably has led to some difference of opinion as to the value to be placed on such drugs as aminophylline (*q.v.*) in the treatment of angina pectoris. Morphine (*q.v.*) often gives relief in a variety of spastic conditions, in part at least, by its tranquillising effect on the patient.

The Cardiac Tonics

The following are used for their direct action on the heart: **digitalis, oubain, strophanthus, quinidine** and, rarely, **squill.**

Digitalis (leaf of *Digitalis purpurea*).

Digitalis owes its action to a mixture of glycosides present in the drug; the most important of these is digitoxin. Other glycosides present include digitalin, digitonin, gitalin and digitalein. Its action on the heart is threefold:

1. It depresses the function of the sino-auricular node as the result of vagal stimulation, thus slowing the heart. This prolongs diastole and increases relaxation, a feature of the therapeutic or first phase of the action of the drug.

2. It depresses conductivity through the bundle of His, etc. During the therapeutic stage of activity this is due to vagal stimulation, but in the later, toxic, stages it results from a direct action on the conducting tissues. In the therapeutic stage this may amount to a partial heart-block, and, in the toxic stage, complete heart-block.

3. The action of digitalis on cardiac muscle is to augment the force of systole in the therapeutic phase and to increase the excitability of the muscle in the toxic stages. The latter leads to extrasystoles, often with coupling of beats, ventricular paroxysmal tachycardia and ventricular fibrillation. Therapeutic doses augment cardiac output if cardiac failure is present, although cardiac output is reduced in the normal heart. This fact, combined with the marked fall in venous pressure, has led to a recent view that the effect of the drug on cardiac output is not due to a direct action on cardiac muscle, but to a peripheral action in diminishing venous return to the auricles possibly by relaxation of venomotor tone.

Digitalis is of value in:

(*a*) **Auricular fibrillation** where its action on the conducting tissues in producing a partial heart-block guards the ventricles from excessive stimulation by the constant stream of feeble auricular impulses. Permitting only some of the impulses to pass, it slows the ventricular rate to within normal limits.

(*b*) **Auricular flutter** where it acts in many cases by increasing the excitability of the auricular muscles as described under (3) above, and so produces auricular fibrillation. If digitalis be then discontinued, the unstable rhythm of fibrillation is, in a successfully treated case, restored to normality. Even if the latter does not occur, digitalis may still be of benefit in slowing the ventricular rate by the partial heart-block to which it gives rise.

(*c*) **Cardiac failure,** with normal rhythm, is benefited by slowing a rapid rate, augmenting systole, prolonging diastole, and diminishing venous return. It thus affords relief of symptoms of heart failure such as dyspnœa, œdema, etc.

An early and important sign of digitalisation is inversion of the T wave and depression of the ST interval in the electro-cardiogram.

In addition to the **toxic symptoms,** indicated above, nausea and vomiting are prone to occur in digitalis therapy. This may originate partially from the irritant effect of the digitalis glycosides on the gastric mucous membrane, partly from direct action on the vomiting centre, and partly as a reflex from the heart itself. If the vomiting interferes with oral administration of the drug it may be necessary to administer it rectally or parenterally. Other toxic manifestations include headache, diarrhœa and disturbances of colour vision. Given in coronary thrombosis, it may have the undesirable effect of increasing blood clotting (see Dicoumarol).

In therapeutic doses, digitalis has little effect on the blood-vessels and blood-pressure, but large doses, by increasing muscle tone, constrict the vessels. In some cases of cardiac failure the blood-pressure may be increased as a result of defective oxygenation of the vasomotor centre. In such cases of "high-pressure stasis" circulatory improvement following digitalisation may lower the blood-pressure as oxygenation of the centre improves. In heart failure, digitalis, in therapeutic doses, increases the urinary output; toxic doses, however, produce oligouria.

The clinical digitalisation of a patient consists in saturating the system with the drug until the full therapeutic effect is achieved or toxic symptoms develop. The total dosage required for this purpose varies, of course, both with the individual and with the number of days required to reach the saturation stage, as the drug is cumulative. A rough but useful guide is the weight of the patient; 1½ to 2½ grains of powdered digitalis daily for each 10 lb. of bodyweight plus 1½ grains for each additional day required to reach saturation. Light adults and children require more of the drug per unit weight, and in these cases the larger recommended dose would be appropriate, viz. 2½ grains daily per 10 lb. Maintenance, following digitalisation, is achieved by giving 1 to 3 grains daily. In severe cardiac failure the dose required fully to digitalise should be introduced in 24 hours, the total dose being divided and given at 6 or 8 hourly intervals, but in less severe cases the treatment may be spread over several days or a week, depending on the degree of failure.

Digitalis Pulverata, Off. ½–1½ gr. repeated; 3–10 gr. single.

Powdered digitalis is standardised and, remaining stable provided it is kept dry, is the preparation of choice for oral or rectal use. It may be prescribed as a tablet, cachet or suppository.

℞ Digitalis Pulv. .. .. gr. i
Ol. Theobrom. .. .. gr. xv
ft. suppos.

Tinctura Digitalis, Off. 5–15 min. repeated; 30–90 min. single.

Tincture of digitalis is intended for inclusion in mixtures, but it is less stable than the powder, especially when diluted as in mixture form.

Infrequently used official preparations are: (1) **Inf. digitalis recens,** single dose 1–4 oz., repeated 90–300 min. (2) **Digitalinum,** subcutaneously, single dose ½–1 gr., repeated $\frac{1}{15}$–$\frac{1}{5}$ gr.). This is a mixture of the glycosides. (3) **Inj. digitalin,** single dose 1–2 ml., repeated dose 0·2–0·4 ml. (4) **Digitoxinum,** $\frac{1}{600}$–$\frac{1}{60}$ gr. (5) *Pil. digitalis co.* (Guy's Pill). This contains 1 gr. each of powdered digitalis, squill and mercury. Proprietary preparations are: (1) *Digitaline,** available as tablets and pills ($\frac{1}{10}$ mg. and ¼ mg.), and solutions for oral and intramuscular use. It contains digitoxin. (2) *Digalen,** a mixture of glycosides, for oral and intravenous use, and as suppositories. (3) *Digifoline,** containing the total glycosides, as tablets and parenteral solution. (4) *Digifortis* (fat-free tincture), as solution and tablets. (5) *Digitunin** (total glycosides), as oral solution and tablets. (6) *Digipuratum** (active principles), as tablets and ampoules. (7) *Digitalone** (fat-free active principles), for oral use. (8) *Digitol** (fat-free tincture), for oral use.

Digoxinum, Off. Initial oral dose, $\frac{1}{60}$–$\frac{1}{40}$ gr.; maintenance dose, $\frac{1}{240}$ gr. twice daily. By intravenous injection, $\frac{1}{120}$–$\frac{1}{60}$ gr.

Digoxin is a stable glycoside obtained from *Digitalis lanata.* Its action is similar to that of the original digitalis (*D. purpurea*) but is developed more rapidly and the drug is less cumulative. For intravenous injection a sterile solution of digoxin in 70% alcohol is available in ampoule form. Each ampoule must be diluted with ten times its volume of normal saline just before use. So injected, the drug is immediate in its action and may be employed in suitable conditions of urgency. Rapid digitalisation can also be achieved by the oral administration of an initial dose of 1·5 mg. ($\frac{1}{40}$ gr.) followed by 0·75 mg. six-hourly. The average therapeutic dose to achieve digitalisation is 3·75 mg. and the average toxic dose is 6 mg. *D. lanata* is employed as a source of the crystalline glycosides, which include digoxin, digitoxin and gitoxin. These glycosides are present in combination with dextrose and an acetyl group, forming the complex glycosides, lanatosids A, B and C. *Cedilanid** is a preparation of lanatosid C. *Digilanid** is a proprietary preparation containing the total glycosides of *D. lanata.* It is available in tablet form for oral use, and in ampoules for injection. The dose of these preparations is the same as for digoxin.

Quinidinæ Sulphas, 3–10 gr.

Quinidine is an alkaloid of cinchona bark. It is optically isomeric with quinine and, like the latter, it possesses antimalarial properties. Quinidine acts as a cardiac depressant, prolonging the refractory period and slowing the conduction rate; its action is directly on the myocardium, but it depresses also the vagal nerve ends. The drug cures about half the cases of auricular fibrillation and some cases of auricular flutter by restoring the normal rhythm. This effect is brought about by a prolongation of the refractory period, which blocks the rapid circus wave of contraction responsible for these states. When quinidine fails to restore normal rhythm it is due to its slowing the rate of conduction sufficiently to allow the muscle tissue to recover from its refractory period; this permits the circus wave to continue. The ventricular rate may be increased during therapy as a result, in part, of the vagal depression. In cases of long-standing auricular fibrillation, where thrombi may have formed in the stagnant auricles, the restoration of normal rhythm and forcible auricular contraction can result in dangerous embolism. Quinidine should not, therefore, be prescribed where there is a recent history of embolism. Nor should it be given in the presence of heart failure because of its depressant action on the myocardium. Such cases should first be treated with digitalis. Quinidine is sometimes useful in abolishing and preventing attacks of paroxysmal ventricular tachycardia. It has also been used in the prevention of extrasystoles. Toxic symptoms are of three types:

1. Those of quinism.
2. Marked tachycardia, extrasystoles, intraventricular block and even cardiac arrest.
3. Embolism.

Idiosyncrasy to the drug may occur and should be tested for by an initial 3-grain dose. Intolerance not being manifest, a *daily* dosage of 15–30 gr. in 3 to 5 divided doses is given, stopping the drug as soon as normal rhythm is restored or intolerance appears. Failure of the therapy after a week's trial is an indication to employ other measures, although occasionally a second course using larger doses, *e.g.* 60 gr., may be successful. In cases which have responded to quinidine therapy, a maintenance dose of 10 gr. daily is given in the hope that the cardiac rhythm will remain regular. The drug is occasionally used intravenously to control paroxysmal tachycardia.

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It has been demonstrated that other substances may have a quinidine-like action on the auricle. Many of these compounds have local anæsthetic properties, *e.g.* procaine, the result of a prolongation of the refractory period of the sensory nerve, akin to that in the auricle. In addition, they reduce the activity of acetylcholine on smooth muscle and are therefore antispasmodics. Pethidine is another example of this class of substance.

Quinina (*q.v.*).

Strophanthus (a seed).

Strophanthus acts qualitatively in the same way as digitalis; it is, however, a very powerful drug and its effects are rapid in onset. It is employed principally when medication is urgently needed, and in cases which are intolerant to digitalis.

Tinctura Strophanthi, Off. 2–5 min.

Strophanthinum, Off. $\frac{1}{240}$–$\frac{1}{60}$ gr. (Strophanthin-K).

This comprises a mixture of amorphous glycosides obtained from strophanthus seeds. It may be injected intravenously in extreme heart failure and, in Continental practice, intravenous medication with strophanthin is preferred to digitalis therapy. The method adopted is to give minimal dosage and repeat hourly until the required effect is produced. Any previous digitalisation of recent origin contraindicates the use of strophanthin, as the cumulative effect may produce dangerous heart-block, etc. *Strophosid** is a preparation of the crystalline glycoside, *k*-strophantosid, which is said to be a more active preparation (1 ml. contains 0·0005 g.).

Ouabainum, up to $\frac{1}{250}$ gr. (Strophanthin-G).

Ouabain is a pure crystalline glycoside from an unofficial species of Strophanthus. It is twice as potent as strophanthin of the Pharmacopœia, and is considered to give better results orally than official strophanthus preparations.

Scilla, 1–3 gr. (a bulb).

The glycosides of squill act on the heart in the same way as those of digitalis. Since the drug is very irritant to the gastric mucosa, however, it is not now employed in cardiology, but only as a stimulating expectorant, and its preparations are not considered of sufficient importance to merit the expense of biological standardisation. *Scillaren,** a commercial preparation, contains the active glycosides.

Acetum Scillæ (Vinegar of Squills), Off. 10–30 min.

Oxymel Scillæ (Oxymel of Squills), Off. ½–1 fl. dr.

Both the above are useful acid expectorants.

Syrupus Scillæ, Off. ½–1 fl. dr.

Tinctura Scillæ, Off. 5–30 min.

The Nitrite Group

This comprises amyl nitrite, sodium nitrite and certain organic nitrates which are reduced to, and exert the action characteristic of, nitrites after absorption.

Amylis Nitris, 2–5 min. by inhalation.

Amyl nitrite is a straw-coloured, volatile liquid which is supplied commercially in fabric-covered, glass capsules containing 3, 4 or 5 minims. When the capsule is broken and the contents inhaled, an immediate but transient selective relaxation of smooth muscle occurs; the effect being produced by direct action on the muscle fibres. There is pronounced flushing of the face and neck due to dilatation of the arterioles, and this migration of blood to the skin vessels causes a rapid fall in blood-pressure which depresses the vagus and gives rise to palpitation of the heart. The cerebral and splanchnic vessels, also, are dilated. Relaxation of the coronary arteries occurs and relief from pain in angina spasm may follow. Inhalation of amyl nitrite sometimes aborts a threatened epileptic seizure, and will afford symptomatic relief in some cases of bronchial asthma. The drug has proved useless in the arteriospasm of intermittent claudication and related conditions, and to relieve "contraction ring" in labour. It is contraindicated in coronary thrombosis because of the low blood-pressure. Amyl nitrite produces its effect within 15 seconds and the action lasts for 7 minutes.

Erythritylis Tetranitras Dilutus, Off. ½–2 gr. (Diluted Erythrol Tetranitrate).

Erythrityl tetranitrate is explosive, and in the official diluted form it is admixed with an equal weight of lactose to obviate this risk.

to 1 mg., have been used to desensitise patients suffering from "cold" urticaria, and the drug has been used intravenously in Ménière's disease.

Oxytocic Drugs

Oxytocic drugs are those which act on the smooth muscle of the uterus, causing uterine contraction.

Ergota.

Ergot is a fungus infesting the ovaries of certain cereal grasses; it is cultivated on rye. Its activity is due mainly to the presence of three alkaloids—ergotoxine and ergotamine, which are soluble in alcohol, and ergometrine, which is soluble in water.

Ergotoxine stimulates motor sympathetic fibres in therapeutic doses and depresses them in larger dosage. Its action is on the myoneural junctions.

Ergotamine acts like ergotoxine, but is thought to act also on inhibitory sympathetic fibres.

Ergometrine (or **Ergonovine**) appears to have some slight stimulating action on motor sympathetic fibres but, unlike ergotoxine, does not depress them in large doses.

Action on the Uterus.

All the alkaloids give rise to powerful contraction, and this is the chief therapeutic effect of the drug. The action is due to stimulation of the motor fibres of the sympathetic; this is a more modern view than that the drug acts directly on the uterine musculature. The effect of ergot is most pronounced on the quiescent muscle as in the puerperium, and it does not increase normally occurring contractions to any appreciable extent. Ergometrine acts rapidly; ergotoxine and ergotamine more slowly, but for a more prolonged period. On account of this action, the principal use of ergot is in obstetrics to control post-partum hæmorrhage, by causing a powerful and prolonged uterine contraction. Ergot, and particularly ergometrine in small doses, has been used in the third stage of labour to stimulate the muscle when uterine pains seem insufficient, but the general view is that such usage is dangerous because a tonic contraction may delay delivery. Ergometrine, or ergot, is also used in subinvolution during the puerperium and to control menorrhagia and metorrhagia, but the danger of toxic effects must be borne in mind, and it is wise to administer the drug only for two or three days at a time.

Action on Vessels.

As a result of their sympathomimetic action, the ergot alkaloids cause vascular, particularly arteriolar, constriction and a rise in blood-pressure. Prolonged use may result in gangrene of the extremities due to arteriospasm, an effect much less pronounced with ergometrine.

Ergotamine, in particular, has been proved of value in the relief of migraine. This effect is not understood, but various theories have been advanced as to the mechanism involved. One is that vasoconstriction relieves cerebral vasodilatation occurring in the later stages of migraine. In migraine attacks the dose is: **oral,** 1–3 mg.; **subcutaneous,** 0·5 mg.

Ergotism.

The toxic action of ergot is usually seen as gangrene of the extremities. Chronic ergot poisoning was formerly common in Europe, due to bread made from rye infested with the fungus, and convulsive ergotism, manifest as spasmodic contraction of the limbs, was common. This effect is thought to be due to ergometrine, which exerts a peripheral action on the uterus resembling that of the other ergot alkaloids but, in addition, has a central stimulating action both on the sympathetic and on the cerebral motoric centres. This central effect can be inhibited by vitamin A or carotene, and in consequence it is not seen except in the presence of dietetic deficiency in these substances, coupled with the administration of ergot.

Ergota Præparata, Off. 5–15 gr.

This is the most stable of the galenical preparations. It retains its potency for a considerable period if kept quite dry. It is administered by mouth in tablets or capsules.

Extractum Ergotæ Liquidum, Off. 10–20 min.

Liquid extract of ergot is reasonably stable when stored undiluted. It should be diluted, with water, only immediately prior to administration, as in the diluted condition it becomes inert very rapidly.

Ergotoxinæ Æthanosulphonas, $\frac{1}{120}$–$\frac{1}{60}$ gr.

Ergotoxine ethanosulphonate may be given orally or by subcutaneous injection.

Ergometrina, $\frac{1}{120}$–$\frac{1}{60}$ gr. orally, $\frac{1}{240}$ to $\frac{1}{120}$ gr. intramuscularly, $\frac{1}{480}$ to $\frac{1}{240}$ gr. intravenously.

Other preparations are the hydrochloride, the acid tartrate and the acid maleate of ergometrine used in similar dosage.

Ergometrine is the alkaloid of choice for use in obstretrics. Methyl Ergometrine (Methergine)* is more potent and less toxic.

Ergotaminæ Tartras (*Femergin**), **oral,** 1 mg.; **subcutaneous,** 0·25 mg.

Dihydro-ergotamine.*

*Dihydro-ergotamine,** a hydrogenated compound of ergotamine, differs from the latter in having a more marked sympathetic inhibitory action and no stimulating effect on plain muscle fibres of uterus and vessels. It is used in migraine and herpes zoster, in parenteral doses of ½–1 mg.

Pituitary (Posterior lobe).

Injectio Pituitarii Posteriosis, Off. 2–5 units: 0·2–0·5 ml.) (*Pituitrin**).

The posterior lobe of the pituitary body contains at least two active principles, the **Oxytocic** and the **Pressor.** The former causes uterine contraction, while the latter constricts blood-vessels, mostly the capillaries, and raises the blood-pressure. In both cases the action is a direct one on the tissues concerned. Uterine contraction occurs within 2–3 minutes of injection and the effect lasts for about 15 minutes. In doses not exceeding 2 units by subcutaneous injection, the solution is employed to induce labour. It may be used, also, during labour to stimulate sluggish uterine movement; both the force and frequency of the contractions being increased. Such use is emphatically contraindicated until the cervix is fully dilated, and also if there is any obstruction, owing to the danger of spasm, delay and uterine rupture. The main use of the extract, however, is for the prevention and treatment of post-partum hæmorrhage, since in full dosage it gives rise to tonic contraction of the uterus. Ten-unit parenteral injections are sometimes employed to stimulate the smooth muscle of the intestine in paralytic ileus; this effect is due to the pressor principle. Combinations of posterior-pituitary extract with adrenaline have been used to raise the blood-pressure in shock, but the clinical results are disappointing. Posterior-pituitary extract antagonises insulin, and may be injected to treat hyper-insulinism.

The extract appears to assist the absorption of water from the tubules, and for this reason it is injected parenterally or used as a snuff to assist in the control of *diabetes insipidus*. Since neither the oxytocic nor the pressor principles *when purified* exert this action, either separately or in combination, another hormone, at present unknown, is assumed to be contained in the extract. The tremendous drawback of posterior-pituitary medication, *especially in the control of diabetes insipidus, is that it is inactive by mouth* and the intranasal method is uncertain, thus parenteral administration is alone reliable. The frequency of dosage may possibly be greatly reduced by injecting an intramuscular depot containing the extract in an emulsified form.

The two principal hormones are available commercially under the proprietary names of *Pitocin** (Oxytocin injection, Off.) and *Pitressin.** The former is useful as an alternative to the official extract (same dosage), and to ergot therapy, in obstetrical use where hypertension exists. Since *Pitressin** (or, for depot therapy, *Pitressin tannate**) exerts the same controlling effect as the official extract in *diabetes insipidus* it is assumed to contain the unidentified hormone to which a previous reference has been made. The dose in *diabetes insipidus* is 0·2 ml. (1 pressor unit) daily.

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Benzylis Benzoas, 5–7 min.

Benzyl benzoate, and other benzyl esters, in common with benzyl alcohol and benzaldehyde, exert a depressant action on smooth muscle. Combinations of these have, accordingly, been used to give relief in bronchial asthma, the spastic stage of whooping-cough, pylorospasm and spastic constipation.

Benzyl benzoate has proved a useful external application in the treatment of scabies. Various emulsified preparations have been devised for this purpose, but in some of them the disperse phase of benzyl benzoate is too coarse to penetrate the acarus burrows. The following is a satisfactory preparation and may be applied with a soft brush:

℞ Benzyl. Benzoat. .. .. ℥i
Sapo. Moll. .. .. ℥i
Spirit. Meth. Indust. .. ℥i
ft. applicat. Shake well before applying.

The patient scrubs thoroughly in a hot bath to open up the burrows before applying the lotion. When the first application has dried a second is made. Often a single treatment on the above lines suffices for a cure.

Narcotina.

Narcotine, a derivative of isoquinoline, occurs in opium to the extent of 2% to 10%. It is seldom prescribed as the isolated alkaloid, but its presence in opium is of importance, as it is the substance chiefly responsible for correcting some of the undesirable actions of morphine. Narcotine stimulates the respiratory centre and relieves spasm of smooth muscle, it thus tends to mitigate the pylorospasm and vomiting associated with the action of morphine. It augments the spinal reflexes after an initial mild depression of cerebral activity, and is said to have some aphrodisiac effect. When relief of spasm is required, papaverine (*vide infra*) is more usually prescribed.

Papaverina Hydrochloridum, Off., 2–4 gr.

Papaverine is one of the isoquinoline alkaloids of opium. It exerts a direct depressant action on plain muscle in spasm but has no action on normal muscle. It is a useful drug for the relief of the paroxysms of angina pectoris, cramp, biliary and renal colic, the spasm of asthma and whooping-cough, arteriospasm (hyperpiesia, intermittent claudication and Raynaud's disease) and vesicle and uterine spasm. The drug has, however, been very much more used in Continental practice than in this country. The central analgesic action of papaverine is very slight and it has no action on the intestinal secretions or on the heart; it has a stimulating action on the respiratory centre. To rest the bladder in acute cystitis, hyoscine or hyoscyamine are usually considered superior. Papaverine sulphate is soluble in water, and may be used orally, rectally or by parenteral injection. Injected into the femoral artery, in doses of ½-2 gr., it may improve incipient gangrene due to arteriosclerosis or *thromboangiitis obliterans*.

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*Depropanex.**

This substance is a deproteinised pancreatic tissue extract, which causes relaxation of smooth muscle. It produces a fall in blood-pressure by its action on the blood-vessels. It is used in the treatment of renal colic. The standard is one depressor unit which produces a fall in blood-pressure equivalent to the rise produced by 0·01 mg. adrenaline; 10 depressor units are contained in 1 ml. The usual dose is 3 ml. i.m. for 4 doses 3-hourly.

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The soluble salts of **barium** exert a powerful stimulating action on striped muscle, and compounds of **lead,** in toxic doses, give rise to spasm of smooth muscle. (See chapter on Metals.)

HISTAMINE AND ANTI-HISTAMINE DRUGS

Histamina.

Histamine (4-(B)iminazolyl)-ethylamine may be derived from histidine (an amino-acid) simply by loss of carbon dioxide; this process takes place during putrefaction. Histamine was found in ergot in 1910 and subsequently its presence has been demonstrated in many plants and it occurs as a normal constituent of the animal tissues. White blood cells contain appreciable amounts and it is even more plentiful in the lungs. Histamine causes contraction of most plain muscle, including the alimentary tract, uterus and bronchioles, the latter resulting in bronchial spasm. The capillaries, however, are widely dilated, and this may produce local œdema of the tissues and a profound fall in blood-pressure with peripheral circulatory failure. Histamine also increases the secretion of many glands, including those of the stomach. When a soluble salt like histamine acid phosphate is injected intramuscularly either in toxic doses or into susceptible individuals, it may cause symptoms resembling those of anaphylaxis with flushing, headaches and, in severe cases, dyspnœa, angina and collapse. Intradermal injection results in an urticarial weal. Histamine may be a factor in the production of symptoms in anaphylactic and allergic states, and in tissue injury by trauma, snake venom, and some chemicals. It is now believed that histamine is present in cells normally insensitive to it, probably in a chemically inactive form by being linked with carboxyl groups in lysine and arginine. In the above-mentioned conditions active histamine is liberated by the splitting of the amino acid-histamine linkage by trypsin and this gives rise to a variety of local and systemic reactions, by acting on the cells themselves or on the mucosa. Tissues most usually involved in allergic reactions are those of the respiratory and gastro-intestinal tract and the epidermis (see also Histaminase, p. 90).

Formerly, these local manifestations were treated by sympathomimetic drugs which gave relief partly by their vaso-constrictor properties and partly because histamine and adrenaline are physiological antagonists. Other symptoms were dealt with by means of spasmolytic drugs. In all these cases, however, the symptoms, only, were relieved: no means was at hand to attack the root cause, viz. the liberation of chemically active histamine in tissues not physiologically equipped to neutralise its properties.

During the past decade there has been introduced a number of synthetic drugs whose fundamental action is to antagonise histamine itself. The mechanism of this action is unknown, but it is believed that the drugs in question may *compete* with histamine for a focus of action in the tissues or of a chemically receptive substance, thus preventing the development of an histamine-like effect on the tissues themselves. Following are some of the chemical agents which have been found by clinical trial to be effective in the relief of many allergic disorders.

It should be stressed, however, that in the case of all the drugs mentioned, the relief is of a temporary character. Thus, although of clinical importance so far as the relief of symptoms is concerned, research is still necessary for methods whereby the root cause of the various disorders can be dealt with in a fundamental manner.

Benadryl* (β-dimethylaminoethyl benzhydryl ether hydrochloride).

This is a synthetic substance belonging to the group of phenolic ethers, of value in various allergic conditions and also relieving spasm of smooth muscle. The anti-allergic action depends upon its being an antagonist of histamine or H substance and it is thus able to prevent the local œdema responsible for these allergic manifestations. *Benadryl** is adsorbed at the site of action of histamine and combines with receptor substance, thus preventing histamine from doing so. In animals, *Benadryl** will prevent histamine effects like anaphylactic shock. Clinically it has been found to benefit: (1) Allergic diseases like hay fever and other types of vasomotor rhinitis, acute and chronic urticaria and angeioneurotic œdema, serum sickness, erythema multiforme, sensitivity to drugs like penicillin and the sulphonamides, and dermagraphism. It may be of some value in eczema, migraine, Ménière's disease, but its action in asthma is uncertain. (2) Spastic states of smooth muscle, particularly dysmenorrhœa, and sometimes spasm of the colon and renal tract. The action of *Benadryl** is palliative and transitory, and recurrence of symptoms may occur when the drug is stopped.

Dosage: One capsule (50 mg.) 3 or 4 times daily. In severe or resistant cases, 6 to 8 capsules daily. At least 2 hours should elapse between doses. The dose for children is calculated on the basis of 2 mg. per lb. bodyweight.

Toxicity: The drug can be tolerated for long periods and is not habit-forming. A few cases show drowsiness, nausea, dry mouth, dizziness and lassitude and sometimes marked disorientation. Such symptoms require temporary reduction in dosage or, rarely, cessation of therapy. Antidotes are stimulants like black coffee, caffeine, ephedrine and, for severe toxic effects, the intravenous injection of histamine 0·5 mg.

*Benadryl** Cream is used for dermatoses produced by local liberation of histamine.

* * * * * *

Neoantergen (*Anthisan**).

This drug, in doses of 0·1 to 0·3 gm. orally thrice daily, is very effective in urticaria and angioneurotic œdema, even when *Benadryl** has failed. It is also of value in hay fever and other types of vasomotor rhinitis. Like other antihistamine compounds it can be used to control sensitivity of reactions to drugs such as insulin, liver and penicillin, being administered ½ hour before an injection of the particular drug. In all these conditions, however, the drug affords only relief of symptoms ; it has no curative effect. Pharmacologically it has also a local anæsthetic action and a quinidine-like effect on the auricle (see p. 79). Toxic symptoms are slight and consist of drowsiness, nausea and headache. *Anthisan** (100 to 600 mg.) has been reported to benefit some cases of bronchial asthma and as the drug sometimes induces drowsiness it may be of clinical importance in nocturnal asthmatic attacks.

Pyribenzamine.

This phenolic ether is less potent than *Anthisan,** but in other respects behaves like the fore-mentioned drugs.

These drugs do not affect the hydrochloric acid content of the stomach or the secretion of gastric juice in response to histamine.[1]

In France, derivatives of thiodiphenylamine are claimed to have an anti-histamine action more powerful and less toxic than the phenolic ethers.

*Antistin.**

*Antistin,** a compound of the imidazoline series, has a similar anti-histamine action to the above and is recommended in the various allergic states. It is of low toxity. The dose is 100 to 200 mg. thrice daily, which can be administered by mouth, intramuscularly or slowly intravenously. As much as 300–600 mg. may be given orally. It has also been found of value in patients showing sensitivity to liver and insulin injections.

Histaminase (*Torantil**).

Histaminase is an enzyme which in the body inactivates histamine by oxidation, and it is because of such inactivation in the gut that histamine is ineffective when given orally. Preparations of histaminase are not active when injected.

[1] Most anti-histamines are antagonistic to acetylcholine and many have a local anæsthetic action.

DIURETICS

A DIURETIC is a substance which increases the output of urine. Physiologically, the hypothalamus controls the activity of the posterior-pituitary lobe and the system regulating water and salt metabolism. This regulation is, in part, effected by the anti-diuretic hormone of the posterior lobe, which, itself, probably acts by increasing the absorption of water from the renal tubules and thus decreasing the urinary output. This hypothalamic-pituitary influence is in part regulated by the tonicity of the blood, as the injection of hypertonic solutions in animals has been found to decrease urinary output, an effect which does not occur if the pituitary gland is removed or the internal carotid artery tied. The hypothalamus is also a centre for heat regulation and control of the autonomic nervous system, and the production of diuresis by cold and by emotion is probably related to these activities. A related factor in the case of cold is, of course, diminished perspiration following constriction of the skin vessels.

Diuresis can also be caused in the following ways:

1. **Intake of excess water** and its elimination by the kidneys. Decreased tubular absorption of superfluous water occurs, and is probably due to a diminished secretion of the anti-diuretic hormone.

2. **Introduction into the tissues by oral, rectal, or parenteral means of salts and other crystalloid solids,** especially those with a low renal threshold. These substances pass through the tubules in solution of which the isotonicity is maintained by osmosis and, in consequence, those with a low threshold value are responsible for conveying to the bladder a larger volume of water than in the case of those with a high threshold, since the latter may be largely reabsorbed into the tissues, together with the water required to keep them in isotonic solution.

3. **Increase in the number of functioning glomeruli.** This may be achieved by circulatory stimulants improving the blood supply of the glomeruli, also possibly by a local action in the case of the purine bases.

4. **Decreased tubular absorption** produced by the excretion of irritants like alcohol or a volatile oil in the glomerular filtrate, and by the use of mercurial diuretics which exert a toxic action on the cytoplasm of the tubular epithelium which temporarily interferes with the concentration of urine.

Cardiac Diuretics

These are drugs used to relieve œdema caused by cardiac insufficiency. Examples are digitalis and strophanthus; for a detailed account of their action the section on Myotropic Drugs should be consulted.

Mercurial Diuretics

The diuretic action of mercury has been referred to in connection with mercurial aperients and in the introductory section of this chapter. Mercurial diuretics are the most powerful available. In consequence of their action on the epithelial cells of the tubules, large volumes of unconcentrated urine are passed into the bladder. Mercurial diuretics are contraindicated in nephritis, and as a working rule constitute unsafe therapy unless the patient can concentrate urine to a S.G. of 1·015 or over. Hæmaturia is always a contraindication. Mercurial diuretics are of value:

1. In cases of œdema due to congestive cardiac failure.
2. In cases of cardiac asthma with or without pulmonary œdema and *even in the absence of general œdema.*
3. To relieve ascites due to liver cirrhosis.
4. To assist in the absorption of fluid in polyserositis.
5. To reduce œdema in cases of nephrosis. This practice is not uniformly approved by clinicians.

Where possible, the diuretic should be administered in the morning so that the night's rest may not be disturbed by diuresis. Owing to the powerful diuretic effect produced by the special mercurial diuretics, it is important clinically to be on guard against dehydration, which can give rise to weakness, anorexia and mental disturbance.

Mersalyl, Off.

This is a complex organic mercurial diuretic which is generally administered by the intramuscular or intravenous route, but suppositories containing it are successfully employed in less urgent cases. Before commencing treatment a small dose is given subcutaneously to test the patient's sensitivity; diarrhœa, skin eruptions and hæmaturia indicate intolerance. When the full dose is given, it should be slowly injected into the vein to prevent thrombosis. Toxic cardiovascular symptoms may occur after intravenous injection, either (1) due to a toxic action on the myocardium when collapse and even death may occur soon after an injection, or (2) the result of a fall in blood volume with a consequent fall in cardiac output, this being due to the diuresis. Symptoms in this latter case are delayed. For these reasons it is probably safer not to employ intravenous medication. The official Injection of Mersalyl, which is the preparation normally employed, should be diluted with sterile normal saline immediately before use. It contains a small content of theophylline, which may enhance the diuretic effect, but is added primarily to prevent ionisation of the mercury and consequent increased toxicity. The oral administration of ammonium chloride concurrently with mersalyl therapy greatly increases the urinary output. This is due partly to salt action, and partly to a reduction of the alkali reserve. The latter appears to reduce the capacity of the tissue colloids to hold salts and water, which tend to diffuse into the plasma, producing hydræmia. The adult dosage of ammonium chloride used for this purpose is 15–30 gr. four times daily (or even 30 gr. 2 hours before the mersalyl injection), preferably administered in a cachet and taken with plenty of water to minimise gastric irritation.

Injectio Mersalyli, Off. 8–30 min. (*Salyrgan,** sim.).

*Salyrgan,** *Neptal** and *Novurit** are proprietary organic mercurials similar in action to mersalyl. Oral preparations of these compounds are available, as well as suppositories of *Novurit.** Oral medication is sometimes useful when the œdema has been reduced by parenteral administration.

The Purine Bases

The purine derivatives used to promote diuresis are the methylxanthines, caffeine, theobromine and theophylline. They are classified as alkaloids; caffeine (theine) occurring in tea and coffee, and theobromine in cocoa. Theophylline is an isomer of theobromine. These bases and their compounds appear to act as diuretics partly by relaxing the renal arterioles and so improving the blood supply and increasing glomerular permeability, and partly by a selective action on the tubular epithelium which has the effect of diminishing water absorption. In addition to their diuretic properties these compounds exert a mild relaxing action on the bronchial muscle and also on certain blood-vessels. The most notable of these are the coronary and cerebral vessels, and purine preparations are used to avert angina spasm, to improve the cardiac circulation during coronary thrombosis, and to relieve migraine and congestive headache. As a diuretic, caffeine possesses the disadvantage that it may give rise to an initial oliguria, thought to be due to its stimulating action on the vasomotor centre leading to a transient arteriolar constriction in the kidneys. It is also unsuitable in the treatment of angina on account of its general stimulatory character. Theophylline is a powerful drug, but with the exception of theophylline with ethylenediamine (*vide infra*) its compounds are irritant and liable to cause vomiting and hæmaturia. Theobromine and its preparations are the most generally preferred of the purine diuretics. For an account of the general actions of caffeine, see "Respiratory, Vasomotor and Circulatory Stimulants."

Theobromina, 5–10 gr. by mouth.

Tabellæ Phenobarbitoni et Theobrominæ, B.P.C. (*Theominal,* Theogardenal**).

Each tablet contains five grains of theobromine and half a grain of phenobarbitone. The tablets are used to tranquillise and relieve patients suffering from hypertension, by central sedation and diuresis, and possibly to effect a direct relaxation of the coronary vessels.

Theobromina et Sodii Salicylas, 10–20 gr. (*Diuretin**).

This soluble compound is more easily diffusible and effective than theobromine alone. **It is too strongly alkaline to administer parenterally.**

Theophyllina et Sodii Acetas, 2–5 gr. (*Theocin**).

This compound has been used orally, but it is irritant to the stomach and to the kidneys.

Theophyllina cum Æthylenediamina (Aminophylline, *Cardophyllin,* Euphyllin**). Oral, 1½–3 gr.; rectal, 5 gr.; intramuscular, 7½ gr. in 2 ml.; intravenous, 3·7 gr. in 10 ml. **The intravenous injection must be made very slowly, 0·1 ml. every second respiration is a safe clinical guide.**

This soluble compound of theophylline is a valuable diuretic; it is very much less irritating than other theophylline compounds, and owing to its solubility and diffusibility it is prompt in action. In addition to its action as a diuretic, theophylline with ethylenediamine is given by mouth to assist in keeping the blood-pressure down and avert angina spasm. It may be injected intramuscularly or, with the precautions indicated above, intravenously to relieve angina and to treat coronary thrombosis. Intravenous medication may also help *status asthmaticus* and renal colic. Intravenously the drug promotes blood-clotting and it has been used successfully in the control of hæmoptysis. In Continental practice it has been advocated as a respiratory stimulant, especially in cases of narcotic poisoning.

A similar compound is theophylline with methylglucamine (*Glucophylline**).

Volatile (or Essential) Oils

These aromatic substances of vegetable origin consist of terpenes (turpentine-like bodies) mixed with varying proportions of aldehydes, ethers, esters, phenols, etc. They possess, in common, antiseptic, carminative, diuretic and expectorant properties. The following are among the principal volatile oils in use:

Oleum Abietis (Pini)	Pine Oil.
,, Anethi	Dill ,,
,, Anisi	Anise ,,
,, Cinnamomi	Cinnamon ,,
,, Eucalypti	Eucalyptus ,,
,, Limonis	Lemon ,,
,, Menthæ Piperitæ	Peppermint ,,
,, Niaouli Depuratum	Gomenol.
,, Santali	Sandalwood Oil.
,, Terebinthinæ	Turpentine.

Applied externally these oils are rubefacient, and certain of them are used in embrocations and other stimulating applications to unbroken skin, for the relief of inflammation and pain, in bronchial catarrh, arthritis, lumbago, etc. The following is a suitable formula for those purposes:

℞	Camphor. Methyl. Sal.	āā 10%
	Ol. Eucalypt. Ol. Pini	āā 5%
	Adipis Lanæ	25%
	Paraff. Molle	ad ℥ij

ft. unguent. stimul.

Various combinations, often with ephedrine and/or adrenaline, are employed in aqueous or oily media to spray the nose in catarrhal conditions, *e.g.*:

℞	Menthol. Eucalyptol.	āā 2%
	Ol. Cinnam.	0·25%
	Paraff. Liq. Leve	ad ℥j

ft. nebula.

Taken internally, volatile oils relieve flatus by promoting local movement of the tract; the following " triple spirit " is prescribed for gastric distension and *globus hystericus*:

℞	Spirit. Chloroform. Spirit. Cajuput. Spirit. Menth. Pip.	āā p. æq.

ft. guttæ.

Sig.: Ten to forty drops to be taken with hot water.

For internal use the oils are nearly always prescribed as spirits, *e.g.*:

Spiritus Menthæ Piperitæ, Off., 5–30 min., or as aromatic waters, such as:

Aqua Anethi	..	Dill Water.
,, *Anisi*	..	Anise Water.
,, *Menthæ Piperitæ*		Peppermint Water.

These waters are frequently used as vehicles for mixtures, and possess the advantages of improving the flavour and preserving the mixture from decomposition by bacteria or moulds. By mouth, the oils exert a sialagogue and afterwards an expectorant action; the latter results partly from gastric irritation and partly following excretion of the oils into the bronchi, where they increase secretion of the glands and excite the ciliated epithelium. In chronic bronchitis, laryngitis, etc., great benefit is derived from the inhalation of oils volatilised by hot water:

℞	Ol. Pini Eucalyptol.	āā ♏xx
	Menthol.	gr. xx
	Tinct. Benz. Co.	ad ℥i

misce fiat inhalatio.

Sig.: ʒi to be added to a pint of very hot water and the vapour inhaled.

The effect of the inhalation is very greatly enhanced if a properly designed inhaler (Nelson type) is employed.

A 5% solution of menthol or gomenol in olive oil is sometimes injected intracheally in bronchiecstasis. Gomenol is occasionally injected into the pleural cavity in recurrent spontaneous pneumothorax (see also sodium morrhuate and silver nitrate).

Stearoptenes

The stearoptenes used in medicine are volatile, crystalline solids which separate from certain of the essential oils on cooling; camphor, menthol and thymol are the most important.

Camphora, 2–5 gr.

Externally, and in small doses by mouth, camphor possesses the general properties of the essential oils, and it is used for its antiseptic, carminative, rubefacient and expectorant action. It is injected as a 20% solution in olive oil, sometimes with ether added, as a circulatory stimulant in pneumonia, etc. The injection is made either subcutaneously, when it is very painful, or else deep into the gluteal muscle. It is controversial whether the stimulation produced of the respiratory and other centres is due to the specific central effects of camphor obtainable from larger doses, or results chiefly as a reflex from the peripheral irritation to which the injection gives rise. The injection of larger doses of camphor cause restlessness, delirium and clonic convulsions by cortical stimulation, especially of the motoric centres. Small oral doses of camphor have a mild aphrodisiac effect due, probably, to hyperæmia of the urethral mucosa during excretion of camphor in the urine. Larger doses, possibly by depressing reflex movements, are anaphrodisiac.

Like menthol, camphor first stimulates then depresses local nerve ends when applied to the skin, so that it gives rise to a sensation of coolness although the vessels are dilated by the axon reflex.

Aqua Camphoræ, Off. ½–1 fl. oz.

This is sometimes used as a vehicle for mixtures, and as an antipruritic application to the skin.

Linimentum Camphoræ, Off. (Camphorated Oil).

For application with friction as a rubefacient. It should be used with great caution in the case of young infants.

Menthol (from Oil of Peppermint or Synthetic), ½–2 gr.

Menthol applied externally produces a feeling of coldness by stimulation of the nerve endings associated with the sensation of cold. There follows a mild degree of anæsthesia due to paralysis of all sensory nerve ends. On this account menthol is rubbed into the skin to relieve frontal headache and neuralgia, and is a component of some analgesic liniments and balms for the relief of rheumatic and allied pain, the irritation of *herpes zoster*, *pruritus ani*, etc. As a cooling liniment in skin diseases the following is suitable:

℞	Zinc. Oxid.	10%
	Mentholis	3%
	Liq. Picis Carb.	5%
	Liq. Calc. Hydrox.	℥iss
	Olei Lini	ad ℥iv
	ft. emulsio.	pro applicatio.

In *herpes labialis* the following application relieves the pain and speedily dries the blebs:

℞	Menthol...	gr. x
	Calamin...	ʒi
	Spt. Meth. Indust.	ad ℥i
	pro applicatio.	

Menthol vapour is inhaled, alone, or with steam, for the relief of respiratory catarrh and sinusitis, and it is a component of many oily nasal-spray solutions.

Nebula Mentholis et Thymolis Composita, B.P.C.

This is used in the treatment of nasal catarrh, but is too strong for many patients. It is better diluted with an equal part of light liquid paraffin.

Thymol (from Oil of Ajowan, etc.), ½–2 gr.

Thymol is a powerful antiseptic resembling phenol in its action. It is more slowly absorbed from wounds than the latter, and is also less irritating and less toxic. It has received extensive trial as an intestinal antiseptic, but with dubious benefit, and, internally, its principal use is as an anthelmintic (*q.v.*). It is employed externally as a parasiticide (10% in alcohol, or a 4% ointment) and in oily and aqueous media (1 : 1,000) to mucous surfaces as an antiseptic.

Glycerinum Thymolis Compositum, B.P.C. (*Glycothymoline,** sim.).

An alkaline solution of thymol with other aromatic antiseptics, for use, suitably diluted, as a mouthwash or gargle, and for douching the nose.

Liquor Thymolis Compositus, B.P.C. (*Listerine,** sim.).

This is used as a mouthwash diluted with one or two parts of warm water. It is applied undiluted to the axillæ as a deodorant.

Thymol Iodide (*Aristol**).

Thymol Iodide is used as an antiseptic dusting powder or ointment.

Karvol.*

This preparation, containing chlor-carvacrol, is used as a mouthwash and gargle.

Miscellaneous Diuretics

Dextrosum (*q.v.*).

Potassii Nitras, 5–20 gr.

Potassium nitrate is rapidly absorbed from the intestine, and, being a non-threshold salt, elimination in the urine is also rapid. It has been used as a diuretic and antipyretic, especially in pneumonia, but it may give rise to renal irritation. The dose should be given well diluted.

Sodii Sulphas.

The cathartic action of sodium sulphate is discussed in the section dealing with aperients. As a diuretic, sodium sulphate is administered usually by the continuous intravenous infusion of an isotonic solution (4·4%) and is employed in the treatment of anuria.

Sucrosum (*q.v.*).

Urea, ¼–4 dr.

Urea is similar in the mechanism of its action to the saline diuretics. In the "urea concentration test" for renal efficiency, the proportion of urea in the urine is determined one, two and three hours after the administration of 15 grammes of urea in 100 ml. of water. At one of these periods the urea content should exceed 2%. Failure to reach this concentration generally indicates kidney damage provided that the volume of urine passed at these periods does not exceed 120 ml. in the first hour and 100 ml. at each of the second and third hours. Chronic interstitial nephritis and other diseases cause marked impairment of the power to concentrate the urine. In doses of 15 gm. thrice daily it is used as a diuretic in the nephrotic syndrome.

Aqueous solutions of urea are decidedly bacteriostatic, and, since they possess a solvent action on protein without irritation of the skin, may be used in the treatment of infected wounds. Solutions, varying from 10% to saturation, are employed to cleanse the wound, and the drug in powder form may then be sprinkled over the affected area, which is afterwards covered with an impervious dressing. Urea may be combined with a sulphonamide, *e.g.* sulphadiazine, when a synergistic effect occurs. A recently introduced proprietary compound termed UFI contains ionisable iodine and urea, and is claimed to be a useful preparation for the treatment of infected wounds and burns. It can be used as a powder or as an ointment, containing 25% of the compound.

Allantoin.

This compound is the diureide of glyoxylic acid and is the active principle of Comfrey root (Symphytum, B.P.C.). It induces cell proliferation and is used as a local application to promote healthy granulations and healing in wounds, burns, skin grafts and ulcers. It may be used as a powder, solution or ointment, and may also be combined with sulphanilamide for an additional bacteriostatic effect.

Other diuretic substances, the actions of which are described elsewhere, include: **Alcohol, Paraldehyde, Thyroid.**

THE VITAMINS

It is only within the last twenty-five years that vitamins have emerged from the status of elusive "accessory food factors" whose gross deficiency was known to lead to pathological changes, to become chemical substances of known composition, exerting very marked physiological and therapeutic activity. To-day it is well recognised that vitamin deficiency, especially that of subclinical severity, is fairly widespread in occurrence and, although due in the main to dietetic deficiency, it may be aggravated by other abnormal circumstances to which the individual is subject. These include infection and pyrexia, chronic poisonings, environmental conditions and gastro-intestinal dysfunction. The increased availability of pure vitamins, and of concentrates containing them, has enabled the clinician to treat deficiency syndromes; it has also opened the door to abuse in the form of self-medication by the public who are led by specious advertisements to regard vitamin therapy as the short road to radiant health! The modern knowledge of vitamin constitution and of their clinical indications entitle them to be regarded as potent drugs to be discriminately employed in states where their value has been adequately proved.

Vitamin A (Axerophthol)

Vitamin A is a fat-soluble alcohol derived from its precursor, the plant pigment carotene. This is converted into the vitamin itself, in the liver of man and animals, where it is stored. It is used medicinally as carotene, in the form of fish-liver oils or in concentrates generally prepared from mammalian livers. The daily requirement is 2,000–6,000 units, the greatest need being in the case of infants and nursing mothers. Dietetic deficiency of the vitamin (or its precursor) results in decrease of the visual purple in the retina, so causing nyctalopia, while gross deficiency may give rise to hyperkeratosis and xerophthalmia, especially in children. Deficiency also predisposes, at least, to a number of other conditions, of which the following are the most important: (i) Urinary calculi, possibly as a result of changes in the tubular epithelium, (ii) Pyorrhœa, (iii) Nervous lesions. In animals suffering from avitaminosis of A, deafness and blindness have been caused by the failure of the bone to grow proportionately with the nerves so that the latter have become mechanically compressed. Some structural breakdown of membranes may occur and facilitate entry of infective organisms; this applies especially to the eyes, the bronchial mucosa and the intestine. The administration of vitamin A will remedy these sequelæ of deficiency, but the treatment makes no other proven contribution to the establishment of tissue resistance to infection in general. Also, nyctalopia due to congenital defects or disease is not benefited. Its use has also been recommended in hepatic disease, where there is defective carotene conversion, in patients on low fat diets, in intestinal diseases such as ulcerative colitis, sprue and cœliac disease where there is defective fat absorption, and also in certain other conditions such as senile vaginitis and Darier's disease of the skin. Large doses of vitamin A (¼ to ½ million units daily) may prove effective in leucoplakia vulvæ. Dilute hydrochloric acid may be given concurrently to aid absorption of the vitamin.

Liquor Vitamini A Concentratus, Off. 1–5 min.

One minim of this solution is equal approximately to 2,500 i.u. of vitamin A.

Liquor Vitamini A et D Concentratus, Off., 1–5 min.

One minim of this equals approximately 2,500 i.u. of vitamin A, and 250 i.u. of vitamin D.

Oleum Vitaminatum, Prophylactic: 30–60 min.; Therapeutic: 40–90 min.

This contains vitamins A and D in a vegetable oil, and is intended as a substitute for cod-liver oil while the latter is in short supply.

Emulsio Olei Vitaminati, 30–60 min.

This emulsion contains 50% of vitaminised oil.

Oleum Hippoglossi, 1–5 min.

Halibut-liver oil contains not less than 30,000 units of A per gramme. The D content varies between 2,500 and 3,500 units per gramme.

Oleum Morrhuæ, Prophylactic: 15–30 min.; Therapeutic: 45–90 min.

Cod-liver oil is well absorbed and readily assimilated. Chemically it is highly unsaturated, this facilitates its metabolism and it is, therefore, a useful "energy" foodstuff. In addition to this advantage the oil contains some vitamin A and a high content of vitamin D. It is, therefore, used specifically in the treatment of vitamin D deficiency diseases such as rickets and osteomalacia, and is of value in tuberculosis and some diseases characterised by malnutrition.

Externally, cod-liver oil has definite bacteriostatic properties possibly due to the presence of peroxides, and it is a useful application for varicose ulcers, bed-sores, inflammatory conditions of the eyes, and for burns. In these conditions the oil soothes pain and stimulates epithelial growth, possibly contributing local nutrition to the cells. In the treatment of burns no coagulation of the damaged tissue occurs, but this is now recognised as an advantage in burns affecting the face and the extremities. A modified *Tulle Gras* dressing in which the wide-mesh fabric is impregnated with soft paraffin, balsam of Peru and cod-liver oil or halibut-liver oil, has proved very useful in the treatment of burns of the hands and face.

Vitamin B.

The B-complex is water-soluble and occurs in the germ of seeds, the husks of rice and corn, in yeast and many other vegetable and animal products. It is most stable in the dry state, but will withstand boiling in water for a short time. Vitamin B_1 is thermo-labile, whilst the vitamin B_2 complex is thermo-stable. Treatment of the latter with adsorbents has resulted in the further separation of some factors which are adsorbed, namely *riboflavin*, *nicotinamide* and *pyridoxin*, whilst the other factors which pass through into the filtrate are *pantothenic acid*, p-*aminobenzoic acid*, *choline* and *inositol*. Good concentrated sources of the B-complex often used in treating deficiency are proprietary yeast extracts such as *Marmite** and *Yeastrel.** Alternative sources are *Benerva Compound,** *Befortiss,** *Betalin Complex,** etc., containing various isolated components of the B-complex in compound tablet or capsule form. These are used in conditions attributed to deficiency of the B-complex.

Aneurinæ Hydrochloridum, Off. (Vitamin B_1, Thiamin, *Benerva,** *Betaxan,** *Crysto-Vibex**).

The substance may be obtained from various natural sources such as rice polishings, or prepared synthetically. The human need is 500 units daily (320 i.u. = 1 mg.). In the tissues aneurin is part of a system of enzyme activity essential for the complete metabolism of carbohydrates, especially in nerve cells. Deficiency of the vitamin results in the accumulation of pyruvates and ketones within the tissues. Complete deficiency causes beriberi, while partial deficiency gives rise to neuritis in varying degree, anorexia, constipation, and intestinal distension which is due to muscular atony and results in auto-intoxication from bacterial toxins. A hæmorrhagic encephalopathy of the Wernicke type may occur. In children, growth may be adversely affected. Deficiency arises from a diet poor in sources of the vitamin, or from increased carbohydrate metabolism (as in pregnancy, particularly accompanied by hyperemesis) making excessive demands upon the tissue content. A similar drain is imposed by the excessive consumption of alcohol and tobacco, and in chronic poisoning by barbiturates, lead, arsenic, etc. Gastrogenic deficiency arises from chronic gastritis of alcoholic or other causation, and from sprue, cœliac disease and intestinal fistulæ, all of which prevent proper absorption of the vitamin. Administration of aneurin will ameliorate or cure symptoms due to its deficiency in the various clinical states enumerated above. Toxic symptoms, although generally absent, have been reported from large doses, particularly when injected. They are either thyrotoxic (nervousness, tremor and tachycardia) or anyphylactic (ranging from sneezing to anyphylactic shock). The usual daily dose, 5–10 mg., should be given orally, except in severe intestinal dysfunction and acute beriberi, when doses of 25–100 mg. may be injected very slowly intramuscularly.

Riboflavin (Lactoflavin, Vitamin B_2, Vitamin G).

Riboflavin is found associated with other members of the B-complex in yeast, green vegetables, milk, liver, eggs and fish-roe, etc. It is essential for growth and it appears to be an important factor in the complex oxidation-reduction mechanism of the tissues. Probable symptoms of deficiency (*ariboflavinosis*) include glossitis with magenta-coloured tongue, a seborrhœic type of skin lesion with desquamation about the lips (angular stomatitis), eyelids, nose and genitalia, depigmentation of the skin and possibly vascularisation of the cornea and retrobulbar neuritis. The syndrome is common in tropical malnutrition and riboflavin deficiency is responsible for some of the symptoms of "kwashiorkor," a tropical nutritional disease of children. Indications for riboflavin therapy are the presence of the above symptoms. In sprue, cœliac disease, tropical malnutrition, etc., it should be given with other members of the vitamin B-complex. The dosage varies from 1 to 10 mg. by mouth or up to 50 mg. by parenteral injection, the latter for severe cases.

Nicotinic Acid (Niacin).

Nicotinic acid occurs naturally with the other components of the B-complex, and deficiency produces pellagra and pellagrinary states which can be cured by giving the vitamin. It forms part of the enzyme systems concerned with the body's reduction-oxidation mechanisms, being essential for the synthesis of co-enzymes in the erythrocytes. It is combined with co-enzymes in the food and in the body tissues. The daily requirements are 12 to 25 mg., the upper limit being desirable in pregnancy and for active workers. Apart from its sources in the diet, it is also synthesised by certain of the intestinal bacteria, and this endogenous production may constitute an important source of the vitamin when there is dietetic deficiency. Other bacteria of the bowel, however, destroy the vitamin. After absorption, nicotinic acid is converted in the blood stream into the amide, **nicotinamide.** The liver in particular contains large amounts, except in liver damage, *e.g.* alcoholism. It is excreted in the urine as nicotinamide methochloride, and also in the milk and sweat, although in deficiency such excretion is reduced or absent. It is an important factor in carbohydrate metabolism, particularly of the central nervous system, and this accounts for the profound clinical and pathological changes found in deficient states. It is also a factor in hæmatopoiesis, and deficiency causes a macrocytic anæmia. Nicotinic acid, but not the amide, has a peripheral vasodilator action, possibly as a result of the release of histamine, causing flushing and sometimes pruritus.

Nicotinic-acid deficiency can occur as the result of deficient intake in the diet, either from economic reasons, fadism, or from ill-balanced invalid diets. It can also occur from defective absorption in gastro-intestinal disease, from deficient storage in liver disease, from defective bacterial synthesis in patients on sulphonamides (see sulphaguanidine) and oral penicillin, and in psychotic states.

Therapeutically nicotinic-acid is used: (1) for its vitamin action, mainly in deficiency states. Here nicotinamide is preferable, because of the avoidance of unpleasant vasomotor effects; (2) for its vasodilator action. Indications for its vitamin action are: pellagra and the pellagrinary syndrome arising in sprue, idiopathic steatorrhœa, colitis and enteric fever. A daily dose of 500 mg. is given orally for 10 days, followed by a smaller maintenance dose. Parenteral administration may be needed if there is vomiting. So administered, it relieves the mental state, glossitis, stomatitis, diarrhœa, dermatitis and anæmia present in these conditions, although the associated members of the vitamin B-complex, ascorbic acid, liver therapy and a diet rich in proteins may also be required to correct associated deficiencies. The vitamin has also been given to some cases of stomatitis and glossitis, particularly when associated with Vincent's infection, as it is thought that deficiency may play some part in the ætiology. In large divided doses of 500 to 1000 mg. daily given parenterally, nicotinic acid is valuable in certain severe psychoses characterised by delirium, exhaustion and coma, which may otherwise prove fatal. These are usually symptoms of an acute deficiency and may follow operations or delivery, when associated with shock, dehydration and deficient diet. Such therapy may also benefit delirium tremens and other alcoholic psychoses. Its use, together with other members of the vitamin B-complex, in sulphonamide therapy is discussed on p. 124. Successes have been claimed for nicotinic acid in the "burning feet" syndrome, high tone deafness, and barbiturate, heavy metal and X-ray poisoning. It is claimed that in diabetes mellitus it improves carbohydrate tolerance and thus diminishes insulin requirements. It is also employed in the treatment of some cases of amenorrhœa and dysmenorrhœa on the grounds that it may stimulate follicular development. As a vasodilator it has been used with occasional success to improve blood supply and relieve symptoms in angina pectoris, Ménière's disease, migraine, Raynaud's disease and other conditions thought to be associated with peripheral arteriolar constriction, *e.g.* chilblains, also in certain cases of asthma, pruritus and rheumatoid arthritis. The dose as a vasodilator is 50 to 100 mg.

Pyridoxine (Vitamin B_6).

Pyridoxine hydrochloride intravenously in doses of 150 to 200 mg. daily has been used with good results in some cases of agranulocytosis, its success being noteworthy in those following thiouracil therapy where response to other measures is not good. Pyridoxine may be used in conjunction with blood transfusions and, if sepsis is present, with penicillin. The drug was first tried out in this type of case because it was found that some patients with anæmia treated with vitamin B_6 developed leucocytosis. Experimentally it is shown to be a growth factor and to influence tryptophane metabolism. Its use has been recommended in disorders of muscle tone and weakness, such as muscular dystrophies and paralysis agitans, in vomiting of pregnancy, in malnutrition and in acne.

Folic Acid.

This is a vitamin B factor found in milk, spinach, liver and yeast. An average mixed diet ensures an adequate intake, the daily requirements being 0·5 to 1 mg. Crystalline folic acid, a yellow substance isolated from liver (the *L. casei* factor) has been synthesised and the name pteroyl glutamic acid given. Other folic acid variants include vitamin M and the "eluate" factor from liver, which like the *L. casei* factor is necessary for the growth of *Lactobacillus casei.* Many animals synthesise free folic acid in the gut. It exercises an important hæmopoietic function and deficiency depresses the formation of red and white cells and platelets. In foods folic acid is present as a conjugate with hexaglutamic acid, known as pteroyl heptaglutamic acid, which is normally broken down in the body into free folic acid. The hæmopoietic function can only be exercised by free folic acid, which is an essential factor for the normal continuation of normoblastic blood formation. Deficiency results in an anæmia in which the bone marrow reverts to the megaloblastic state. In such megolablastic anæmias the administration of free folic acid will induce a successful remission, similar to that produced by liver therapy, together with an excretion of free folic acid in the urine. Synthetic folic acid, which is in the free form, has been used therapeutically in the following megaloblastic anæmias: (1) Addisonian pernicious anæmia. Here there is a failure to liberate free folic acid from its conjugated form, the factor responsible for this liberation being the hæmopoietic or liver principle which, of course, is deficient in this disease. This explains the mechanism of therapy with liver preparations.[1] These do not act by virtue of their folic acid content, which is only minute. This view with regard to the mode of action of folic acid is not accepted by some authorities, who regard the substance as an enzyme concerned in the formation of the anti-anæmic principle. Cases of pernicious anæmia receiving folic acid may develop subacute combined degeneration which, however, will respond to concentrated liver therapy, suggesting that liver contains separate factors responsible for the integrity of the central nervous system.[1] In view of this finding, folic acid should only be used in pernicious anæmia in patients sensitive to liver preparations before they are desensitised, or as a temporary measure in the initial stages. (2) Nutritional macrocytic anæmia, in which the intake of conjugate folic acid in the food is deficient. (3) Sprue syndrome, in which there is failure to absorb the conjugate. In sprue, improvement in the blood picture only occurs during the stage when the bone marrow is megaloblastic, but beyond this stage the anæmia remains refractory. In this disease as well as in other cases of chronic diarrhœa there is a rapid improvement in intestinal function with subsidence of the diarrhœa, often preceding or occurring in the absence of hæmatological response, suggesting that folic acid has an independent action in controlling alimentary function. (4) Pernicious anæmia of pregnancy, idiopathic refractory megaloblastic anæmia (achrestic anæmia), pellagra and megaloblastic anæmia of infants. In these diseases there is generally a failure to respond to purified liver extracts, and free folic acid may be effective in some of the cases where the deficiency is produced either by an inadequacy in the diet or a failure in absorption. The fact that oral liver or proteolysed liver may be more effective than folic acid in these refractory cases suggests that other factors apart from folic acid and the liver principle are necessary for the final stages of normal blood formation. In fact there is evidence that there may be an additional reticulocytogenic factor present in liver necessary for the production of reticulocytes. (5) Aplastic anæmia does not usually respond to folic acid, although improvement has been claimed with massive doses of 200–400 mg. daily.

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[1] Spies, who has obtained a therapeutic response with conjugated folic acid in pernicious anæmia, believes that the liver and kidneys may contain the enzymes necessary for the liberation of free folic acid.

Granulocytopenia and thrombocytopenia, unless a symptom of deficiency in one of the above diseases, does not respond to folic acid treatment. The latter has no therapeutic value in anæmias in which the bone marrow reaction is normoblastic, nor is it very effective in cœliac disease or ulcerative colitis.

Dosage: both for initial and maintenance therapy, doses of 5 to 20 mg. daily appear adequate, but increasing doses may become necessary. Oral therapy is usually effective, but parenteral administration may be an advantage in the early stages of sprue. If the blood picture does not return to normal, supplementary therapy with oral liver extracts or proteolysed liver is necessary. If there is no improvement after two weeks, continued folic acid treatment is useless. Folic acid can be discontinued as soon as the blood picture is normal in pernicious anæmia of pregnancy and nutritional macrocytic anæmia, but needs to be permanently administered in idiopathic refractory megaloblastic anæmia. There are no toxic symptoms with oral doses, although histamine-like reactions can occur with massive intravenous dosage.

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[1] Neurological disease can appear in pernicious anæmia, when folic acid is given, even when this is supplemented by liver therapy. This is due either to folic acid by virtue of an *l*(+) glutamic acid group blocking the utilisation in the central nervous system of a chemically related metabolic factor (see p. 115) or to the fact that excess of folic acid leads to associated deficiency of other members of the vitamin B-complex.

Thymine (5 methyl uracil).

This compound, in doses of 15 gm., has a similar action to folic acid, and the latter may help to synthesise thymine in the building up of nucleic acid.

Pantothenic Acid.

This occurs as an oil of which the calcium salt, a solid, is used clinically. It is present in most animal tissues, particularly liver and heart. The vitamin appears to be closely associated with riboflavin metabolism, and it may be deficient as a result of severe malnutrition associated with ariboflavinosis. Glossitis and cheilosis in such cases may respond to treatment with calcium pantothenate, and the latter has also benefited primary nutritional achromotrichia, an African nutritional disease affecting children, in which there is greying of the hair and marasmus. The dose of calcium pantothenate is 25–100 mg. daily, and the drug can be given orally or by injection.

Choline.

This substance is present in part in the normal diet and in part is derived from methionine (*q.v.*), which provides the necessary labile methyl groups. The daily intake in the diet is about 500 mg. Choline deficiency like methionine deficiency results experimentally in fatty infiltration of the liver, and its administration has been shown to diminish the effects of liver damage, particularly when given with methionine.[1] Choline has been given orally in doses of up to 6 g. daily in conjunction with a high protein-carbohydrate-vitamin B diet in cirrhosis of the liver. In the hepatorenal syndrome following severe hepatitis, choline chloride has been injected intravenously by the drip method in doses of 4–8 g. daily. The drug has been recommended in paralytic ileus, the dose being 0·6 gm. by intravenous drip. Slowing of the heart and a fall in blood-pressure can occur as with acetylcholine (*q.v.*).

P-aminobenzoic Acid.

For the physiological functions and therapeutic application of this substance see p. 124.

Inositol.

Experimental deficiency of this isomeride of cyclohexanehexol causes loss of hair, dermatitis and fatty liver, and it appears necessary for growth and normal peristalsis. It has possible uses in skin diseases and with α-tocopherol in muscular dystrophies. The dose is about 100 mg.

Vitamin C (Acidum Ascorbicum, *l*-Ascorbic Acid).

Ascorbic acid is found naturally in fresh fruits, including oranges and black currants, also in green vegetables, rose hips, etc., and it occurs in large quantities in the suprarenal cortex. The vitamin is also made synthetically. Cooking in the presence of air or alkali speedily effects its destruction, but if air is excluded, as in modern canning processes, the vitamin remains unaffected. Babies on dried and other artificial milk feeds need supplementary vitamin C administration. It appears to be a component of the mammalian oxidation-reduction system, but its most important function is the control of the formation of colloidal intercellular bodies, such as cement substances in the capillary walls, dentine, cartilage and the matrix of bones. The minimal requirement is about 25 to 30 mg. daily, but optimal requirements, particularly for children, are probably double this amount. The need is increased during pregnancy and lactation, and for those doing heavy work. Normal adults on satisfactory diets excrete 15 to 30 mg. daily in the urine, but the undernourished individual retains the vitamin in the tissues until these are saturated and the deficiency made good. The excretion of ascorbic acid in the urine enables it to be estimated by its ability to reduce and so decolorise a blue dye, dichlorphenol-indophenol. Any deficiency can be assessed by this method following a test dose of 300 mg. of ascorbic acid.

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[1] Substances which, like choline and methionine, prevent excessive fat deposition in the liver with subsequent fibrosis, and which aid liver cell regeneration when these states are present, are termed *lipotropic factors*.

Gross deficiency results in scurvy in which the large hæmorrhages are due to capillary breakdown. The petechiæ are, however, thought to be due to the lack of associated vitamins (vitamin P, hesperidin and citrin) usually found with naturally occurring C (see later). Anæmia in scorbutic states is due to the lack of the normal stimulus which ascorbic acid gives to the bone marrow for erythropoiesis. Although gross deficiency is now uncommon in Britain, it is suggested that subclinical states due to less marked deficiency is more frequent, and responds to treatment with the vitamin. Minor deficiencies of this type show themselves by such symptoms as hypertrophied and bleeding gums, sometimes with gingivitis and Vincent's infection, anæmia, lassitude, increased liability to infections, increased tendency to hæmorrhages following stresses and injuries, and in children to developmental defects affecting the bones and teeth. Benefit which has followed its administration in cases of menorrhagia or hæmaturia, without any apparent underlying organic disease, may also be due to the fact that these conditions are due to deficiency. Conclusive evidence of the effect of the vitamin in other clinical conditions is lacking, but there is reason to believe that it plays a not unimportant part in reducing the incidence of infections and promoting the healing of wounds and fractures. It is employed therefore in the treatment of such infections as tuberculosis, pertussis, pneumonia, rheumatism, diphtheria, etc. Apart from its value in scorbutic hypochromic anæmia, it has been of value in some cases of pernicious anæmia resisting liver therapy. Dietetic deficiency can arise from inability to obtain the necessary foodstuffs, or from various dyspepsias (*e.g.* gastric ulcer), or infections in which the diet allowed may contain insufficient quantity of the vitamin. In infections, moreover, there may be increased excretion of the vitamin. In all such cases large doses of vitamin C should be administered. Ascorbic acid has a diuretic action and has been used for this purpose in heart failure. It has been given during labour on the grounds that it may have a synergistic effect on posterior pituitary extract. It is also claimed to be of value in allergic diseases such as urticaria, hay fever and asthma, as well as in skin diseases like eczema, psoriasis and erythema multiforme. Its administration to cases of keratitis and other conditions affecting the cornea and lens is based on the large amounts of ascorbic acid normally present in these structures as well as upon the fact that experimental deficiency in animals produces cataracts. Its reducing action has led to its use as a detoxicating agent in poisoning due to arsenicals, gold, lead and sulphonamides (see also p. 66).

The vitamin may be administered in a natural form medium, *e.g.* orange juice, etc., or as ascorbic acid, the usual dose employed being 50 to 100 mg. daily by mouth. Much larger doses can be employed when there is deficiency, and ascorbic acid may also be injected parenterallv when absorption is defective.

Vitamin P.

This vitamin, found associated with ascorbic acid in paprika, rose hips, oranges and lemons, prevents excessive capillary permeability. Although it has not been isolated in pure form, compounds have been prepared which, experimentally and clinically, are able to correct lowered capillary resistance. There is still considerable difference of opinion regarding their effectiveness. **Hesperidin** (*Permidin**) is a crystalline flavonone glycoside, insoluble in water. It is used in doses of 900 mg. daily in hæmorrhagic diseases associated with capillary damage. **Citrin** prepared from oranges and lemons is water-soluble. It has been suggested that it contains hesperidin and its derivative termed eriodictin, but this view has been contested on the grounds that hesperidin is insoluble in water. **Rutin** is a flavanol glycoside derived from buckwheat and tomato stems. It is a crystalline substance and is given in doses of 120 mg. daily to control increased capillary fragility in hypertension, including those cases undergoing thiocyanate treatment, in hæmorrhagic telangiectasis and in poisoning due to drugs. More recent compounds, derivatives of hesperidin and of epicatechin, may prove to exert even greater vitamin P activity.

Vitamin D.

Several closely related substances are known which exert a profound antirachitic activity. The two most important members of the group are D_3, which is found in fish and mammalian livers, butter, eggs and milk, and can be made by the U.V. irradiation of 7-dehydrocholesterol, and D_2 (Calciferol), which is prepared by the U.V. irradiation of ergosterol. Calciferol does not occur naturally. The main action of vitamin D is to promote absorption of calcium and phosphorus from the gut. Deficiency makes the intestinal contents more alkaline, and this diminishes absorption of the elements concerned with a resulting increased content in the fæces and a decrease in the blood. There is evidence, also, that the vitamin acts directly on the bones. The combined effect of the action of D is to ensure normal ossification. Deficiency results in the formation of an excess of osteoid tissue with inadequate ossification and enlargement of the epiphyses and other rachitic manifestations. Other deficiency manifestations are osteomalacia, defective enamel and dentine in teeth and tetany and the other manifestations of spasmophilia (due to low blood calcium). Insolation, or the exposure of the skin to U.V. irradiation, supplies the organism with a large proportion of the D_3 necessary to health, the balance must be supplied by adequate diet. Apart from the clinical indications arising from the conditions outlined above, there is especial need of vitamin D in infancy, during the periods of pregnancy and lactation, and in old age as a preventive of osteoporosis. It is used, also, in large doses in conditions where absorption is subnormal, as in sprue, cœliac disease and idiopathic steatorrhœa. It is considered helpful in chilblains. By increasing calcium absorption it may assist the healing of fractures.

Dosage.—One i.u. corresponds to 1 mg. of the standard solution of irradiated ergosterol. The average daily dosage recommended is: 500–600 i.u. for children; 400–1,200 i.u. for adults.

Liquor Calciferolis, Off.

This contains 10,000 i.u. per gramme, dissolved in vegetable oil.

Calciferol.

Calciferol in large doses of 100,000 units daily stimulates connective tissue formation and is of value in the treatment of lupus vulgaris, tuberculous glands with sinuses and possibly other forms of surgical tuberculosis, but not of pulmonary tuberculosis. Toxic symptoms may result, such as nausea, vomiting, anorexia, lassitude, and there may be severe symptoms of impaired renal function such as drowsiness, aphasia, confusion and convulsions, with a rise in blood urea and blood pressure. The drug is contraindicated if there is renal damage and arteriosclerosis; if the blood calcium rises unduly, and there are toxic symptoms, the drug may have to be stopped. Calcification in the heart, blood-vessels and bronchi may occur. Arterial calcification, as an untoward effect, has been well ventilated in the medical press. Rarely there may be dissemination of a tuberculous focus.

Dihydrotachysterol (*A.T.* 10*).

This is a stable, oil-soluble fraction of irradiated ergosterol containing no vitamin D. It is of value when administered orally in the treatment of parathyroid tetany, as after thyroidectomy, since its action is to increase the calcium ion content of the blood. Its action is prolonged and no tolerance develops. The dose of the oily solution is 1–6 mil. weekly, dosage being controlled by the calcium level of the blood.

Vitamin E (Tocopherylis Acetas, B.P.C., *Phytoferol,* Ephynal,** sim.).

Vitamin E is found naturally in wheat-germ oil, in the embryos of other seeds, in certain nuts, in lettuce, eggs, butter and milk. Experiments with rats and on cattle suggest that vitamin E is essential for the secretions of the anterior-pituitary gland to be maintained at normal. The experimental data tends to show that, in pregnancy, E-avitaminosis leads to the early death of the fœtus; a minimal intake may enable the young to be born alive, but early in life severe neuromuscular lesions, including paresis of the limbs, develop. These lesions can be cured by the administration of vitamin E, but the clinical application of the vitamin in muscular dystrophies has been disappointing. It has been used, however, with good effect in some cases of vulvovaginitis, ***pruritus vulvæ*** and œstrogenic hypoactivity, and it is said, also, to act as a galactagogue. In the male, deficiency leads to degeneration of the seminal epithelium and eventual irreversible sterility. Oligospermia and undescended testes may respond to E therapy. These effects on the gonads and related glands result probably from stimulation of the anterior-pituitary body.

Dosage.—The i.u. is defined as the amount of vitamin E equivalent in specific activity to 1 mg. of synthetic racemic alpha-tocopherol. The human requirement as to dosage is not fully known, but is stated to be of the order of 3 mg. daily, or 1–2 gm. during a complete pregnancy. Where there is a history of previous abortion, larger doses are necessary, and for threatened abortion 30 to 60 mg. daily, combined with progesterone (*q.v.*), should be prescribed. For menopausal symptoms such as flushes and depression, 10 to 30 mg. daily are given. It has the advantage in this condition of not causing excessive uterine bleeding such as sometimes occurs after œstrogens. Large doses (200–300 mg. daily) have recently been given for peripheral vascular disease, including thrombosis and gangrene, and in the collagenoses, such as lupus erythematosis.

Vitamin K.

Acetomenaphthonum, B.P.C., $\frac{1}{6}$–1 gr. orally.
(*Kapilon**—oral, *Prokayvit**—oral.)

Menaphthonum, B.P.C., $\frac{1}{12}$–$\frac{1}{6}$ gr. intramuscularly.
(Mendione, *Kapilon,** *Prokayvit.**)

Vitamin K occurs naturally in a great variety of green plants, of which spinach and lucerne (alfalfa) are the richest sources. This form is known as vitamin K_1. Cabbage and cauliflower also have a high content. Liver oils, tomatoes and potatoes have small quantities present. It is synthesised by bacterial action in the intestine of men and mammals, this variety being vitamin K_2. A number of analogues have beeen prepared possessing typical K activity, these are all derivatives of naphthoquinone. Menaphthone is 2-methyl-1 : 4-naphthoquinone, and acetonaphthone is diacetyl-2-methyl-1 : 4-naphthohydroquinone. Vitamin K is specifically necessary for the formation of prothrombin in the liver. If insufficient is absorbed, there is a marked prolongation of the clotting time of the blood and a corresponding tendency to severe hæmorrhage from any slight cause. Since the vitamin is fat-soluble, any cause which interferes with fat absorption leads to K deficiency in the tissues, *e.g.* lack of bile in the gut from obstructive jaundice, where its administration is particularly useful preparatory to operation, cœliac disease, sprue, ulcerative colitis, the habitual use of liquid paraffin as a laxative, etc. The new-born are usually deficient in K, and administration of this vitamin to expectant mothers is recommended as a routine to obviate the hæmorrhages to which newly born infants are liable. It is used also in the treatment of some cases of neo-natal hæmorrhage, but the results are by no means uniformly successful. Some cases of chilblains are benefited but, in general, nicotinic acid (*q.v.*) is more useful.

It has proved useful in some types of chronic urticaria with a prolonged prothrombin time, possibly because the formation of fibrin is necessary for the protection of the capillary endothelial wall. It has also been given in some cases of menorrhagia thought to be due to disturbance of liver function preventing inactivation of œstrin. Russian investigators suggest that the vitamin may have a wider physiological function than prothrombin formation, and that it may affect other blood components necessary for blood-clotting, such as fibrinogen, and also influence the active mesenchyme of connective tissue. They claim that it may be of value in bleeding other than that due to hypoprothrobinæmia, and that it may help in the healing of wounds.

Dosage: 1 gm. of vitamin K is equivalent to 12 million chick-curative (Dam) units. If an oral preparation is used, the daily dose of 10 mg. is usually adequate, but 30 mg. or more have been used where absorption is impaired. If employed orally in obstructive jaundice the concurrent administration of bile salts is necessary. For intramuscular injection an oily solution is used, containing 5 mg. per ml. This dose may be injected daily for 3 days to patients with obstructive jaundice undergoing an operation, or be given as a single injection to pregnant women just before delivery, or to the newly born infant. As these injections are painful, an oral dose of 10 mg. to the mother 2 hours before delivery is effective. A preparation suitable for intramuscular intravenous administration is *Synkavit,** a naphthohydroquinone derivative.

HÆMOPOIETIC SUBSTANCES

THE substances necessary for normal red blood cell formation (erythropoiesis) are:

1. **Iron** (*q.v.*) and a trace of copper; the latter promotes utilisation of the iron in the formation of hæmoglobin.

2. **Vitamin.** Ascorbic acid (*q.v.*) appears to act as a general marrow stimulant. The rôle of the vitamin B-complex in respect of erythropoiesis is uncertain. It is no longer regarded as being associated with the extrinsic factor (see below). Nevertheless the B-complex (often administered as *Marmite** or *Yeastrel**) is of value in the treatment of some macrocytic anæmias, and an important new hæmopoietic factor has been discovered in folic acid (*q.v.*). The anæmia of pellagra can be cured by nicotinic acid and that of beriberi by aneurin.

3. **Thyroid** (*q.v.*). The thyroid gland acts mainly as a metabolic stimulant and it is necessary in the treatment of anæmias associated with hypothyroidism.

4. The Hæmopoietic or Liver Principle.

This is produced by the interaction in the alimentary tract of two separate entities: the **extrinsic factor**, largely found in meat (particularly beef) protein, and the **intrinsic factor**, probably an enzyme produced by the pyloric end of the normal stomach, and present in normal gastric juice. The haemopoietic principle is absorbed from the intestine and stored in the liver. It is an amino-acid combination resembling a peptide, comprising a primary and three accessory factors. The latter, inactive by themselves, enhance the primary factor.[1] It is essential as a stimulant to the bone marrow for the normal maturation of red cells. Deficiency of this principle results in failure to mature red cells and a consequent deficiency of normal adult red cells in the blood. This comprises pernicious anæmia. Pernicious anæmia and anæmias similar to it can be caused by:

(1) **Gastric abnormalities,** here the stomach no longer produces the intrinsic factor on account of constitutional defect of the gastric mucosa, chronic gastritis, the pernicious anæmia of pregnancy, and operations on the stomach. The first two causes account for most cases of pernicious anæmia.

(2) **Interference with absorption of the hæmopoietic principle,** viz. steatorrhœas such as sprue or cœliac disease, bothriocephalus tape-worm infestation, intestinal fistula and ulceration.

It should be noted, too, that the hæmopoietic principle is necessary for the normal nutrition of the spinal cord, and in its absence subacute combined degeneration of the cord results (see p. 103).

The anæmias described above can be effectively treated by the administration of extracts from the livers of healthy animals, which contain the hæmopoietic principle. Some liver preparations are given orally, but it is generally the practice to use an extract prepared for parenteral administration, as these are more economical and more effective, particularly where absorption from the tract is impaired. The therapy can be augmented, where response to liver extracts is not satisfactory, by the concurrent administration by mouth of an extract of hog's stomach containing the intrinsic factor. These measures will sometimes help in the treatment of subacute combined degeneration of the cord, of pellagra, cœliac disease and possibly of disseminated sclerosis.

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[1] A red crystalline substance termed vitamin B_{12} has been isolated, and is believed to be the actual hæmopoietic principle. It is effective in doses of 2·5 to 20 μg.

Treatment with liver consists, in the first place, of intensive therapy designed to produce a rapid rise in the red cell content of the blood. Subsequently, maintenance doses are given at intervals of 3–4 weeks, and have to be continued in true pernicious anæmia for the remainder of the patient's life, as the failure to produce the intrinsic factor is permanent.

The first phase of treatment can be by intramuscular injection, but in urgent cases intravenous medication with a suitable preparation may be used. For maintenance, intramuscular therapy is usually adopted. Reactions following injection are rare but, particularly with intravenous injection, collapse, urticaria, vomiting and dyspnœa (protein shock) may occur. Recently it has been shown that these reactions may be due to sensitisation to liver extracts,[1] and desensitisation can be carried out. A favourable response to liver and stomach therapy can be observed and assessed by the appearance in the blood of numerous reticulocytes.

Some of the more important commonly used preparations are tabulated below, together with the average dosage recommended (mainly after Whitby and Britton):

Intramuscular Preparations	**Initial Dosage**	**Maintenance**
*Anahæmin** ..	2–4 c.c. weekly.	2 c.c. monthly.
*Anahepol** ..	do.	do.
*Campolon** ..	2–5 c.c. on alternate days until red cell " count " is 3 million, then weekly until the " count " is normal.	3–5 c.c. fortnightly.
*Examen** ..	As *Anahæmin**.	
*Hepastab** ..	As *Campolon**.	
*Hepatex-T.** ..	As *Campolon**.	
*Neohepatex** ..	1–2 c.c. for 3 days, then 2 c.c. every 7–10 days until the " count " is normal.	1–2 c.c. at 1 – 4 weekly intervals.
*Plexan** ..	2 c.c. daily until good reticulocyte response and then 2–4 c.c. weekly	2–4 c.c. monthly.
Intravenous Preparations		
*Hepatex P.A.F.**	5 c.c. daily for 2–10 days depending on severity and response.	Not used for maintenance.
*Neohepatex** ..	As Neohepatex I.M. In very severe cases 4–6 c.c.	As Neohepatex I.M.
Hepastab No. 2 ..	As *Neohepatex*	

In clinical practice it is usual to differentiate the parenteral preparations into two groups: the first comprising *Anahæmin,** *Anahepol,** *Examen,**

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[1] These sensitisation reactions are benefited by anti-histamine drugs (see p. 88).

*Neohepatex,** *Hepastab* No. 2, *Hepatex P.A.F.,** *Pernæmon Forte,** which are highly purified and concentrated preparations containing only the pernicious anæmia factor; and the second, which includes *Hepalon,** *Campolon,** *Hepatex,** *Heparglandol B,** *Plexan** and *Prœthron,** which are termed "crude" preparations in the sense that they more resemble total extracts of liver, and some of them may be fortified by the addition of aneurin, etc.

The former group is generally employed in typical cases of uncomplicated pernicious anæmia, whereas if the case is atypical (see p. 103), or complicated, a preparation from the second group is usually preferred. The latter group is employed, also, in the other conditions mentioned above as suitable for liver therapy and the term "polyvalent" is sometimes used to describe these "crude" extracts. Whilst these cruder extracts may prove of some value in the refractory group of megaloblastic anæmias, they are inferior in this respect to proteolysed liver and folic acid (*q.v.*).

Oral Preparations

Extractum Hepatis Liquidum, Off. (*Livadex** oral).

1 fl. oz. is equivalent to about half a pound of fresh liver.

Proteolysed Liver (*Hepamino**).

Proteolysed liver is obtained by the controlled digestion of *whole* liver with papain. It contains the anti-pernicious anæmia principle, folic acid, biotin, riboflavine, predigested proteins, and copper and iron. It is a granular, brown, slightly hygroscopic powder, soluble in water. It is administered orally and is of value in the treatment of various types of megaloblastic anæmia. It is recommended for those cases of pernicious anæmia where the patient shows sensitivity to liver injections, or objects to these, or where it is difficult to ensure their regular administration. Oral proteolysed liver has been found of particular value in the treatment of megaloblastic anæmias refractory to parenteral liver, *i.e.* in achrestic anæmia (idiopathic refractory megaloblastic anæmia), pernicious anæmia of pregnancy, sprue and nutritional macrocytic anæmia. In these refractory cases it has been noted that highly fractionated liver extracts are relatively ineffective because of the loss of important active principles and that even cruder extracts may not be adequate in controlling the anæmia (see also folic acid). While oral whole liver extract is effective in these patients, its unpalatability, as well as the impaired digestion and powers of absorption frequently present, make predigested proteolysed liver preferable.

The initial dosage is 1 or 2 tablespoonfuls daily. The minimum maintenance dose is 2 teaspoonfuls daily.

Proteolysed extracts of liver are also available, such as the fluid *Hepatex oral,** *Neohepatex** and *Hepatex T,** the latter two being for parenteral administration. It is suggested that proteolysation liberates, and thus increases the potency of, the active hæmopoietic principles.

Ventriculus Desiccatus, B.P.C. (*Eugastrol,** *Gaster Siccata,** *Ventriculin,** sim.).

The initial dose of dried stomach powder is one ounce daily until the blood count is normal, it is then reduced to maintenance dosage.

Desiccated Pigs' Intestine (*Ileum Desiccatum**).

Intestinal mucosa from pigs' small intestines have been used either in the raw state or desiccated and defatted, the latter in doses of 1 oz. daily in the treatment of ulcerative colitis. It is suggested that the improvement which may result in some cases may be due to the rectification of a deficiency.

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Pyridoxine (*q.v.*).

Cerevisia (Yeast).

Yeast was originally used on account of its supposed value in assisting digestion. It is recognised now as a source of the vitamin B complex and is administered in conditions associated with vitamin B deficiency (see also *Marmite*). Yeast is rich also in nuclein, and on this account it is prescribed for the treatment of boils, etc., as a stimulant to leucocyte formation.

Sodium Pentose Nucleotides (*Pentide,* Pentnucleotide**).

The further investigation of the stimulating action of nuclein on leucocyte production, mentioned in the preceding monograph, led to the discovery that the sodium pentose nucleotides could be administered intravenously or intramuscularly with hæmatological and clinical improvement in agranulocytosis and related conditions, *e.g.* after sulphonamide or gold therapy. The usual daily intramuscular dose is 10 ml. of an 8% solution in normal saline. The same quantity diluted with normal saline to 100 ml. is employed intravenously when a rapid response is necessary. Occasional toxic reactions, including anginal pain, may follow intravenous medication.

DRUGS DEPRESSING HÆMOPOIETIC FUNCTION

In leukæmia and polycythæmia, drugs are given to reduce the abnormal activity in the hæmopoietic tissues, and the majority of these drugs act by depression of the bone marrow. Arsenical Solution (*q.v.*) in doses of 5 minims thrice daily, increasing gradually to the limits of tolerance, may be given in both the above conditions. Benzol has been employed in leukæmia, but is liable to produce aplastic changes in the bone marrow. X-ray therapy is the commonest and most useful method of treatment for these diseases. Radium, also, has been employed for leukæmia. In all cases dosage must be carefully controlled so as to avoid excessive depression of the marrow with severe anæmia. Many drugs may act as marrow depressants and cause anæmia, sometimes progressing to the aplastic type, or agranulocytosis, or both; in addition to the above drugs may be mentioned the organic arsenicals, the sulphonamides, gold, amidopyrine, bismuth, thiouracil, etc. See also radioactive phosphorus and nitrogen mustards.

Phenylhydrazine Hydrochloride.

This drug is used in the treatment of polycythæmia, its main action being to damage the red cells so that they are more easily hæmolysed. There may be some depression of the bone marrow. The risks of therapy with the drug are the possibility of a very rapid hæmolysis of red cells or the onset of thrombosis. Contraindications to its use are patients over sixty, those with arteriosclerosis, liver or renal disease, or the bedridden. During treatment, massage of the legs will diminish the risk of thrombosis. The drug is given orally in capsules. The dose recommended is 0·1 gm. twice daily, up to a total of 3 gm. As the drug is cumulative, a rest of 10 days is necessary. If the blood count has not fallen to between 5 and 6 million per cmm. at the end of this period, a further course up to a total of 1 gram may be given. A subsequent maintenance dose of 0·2 to 0·4 gm. weekly, or less frequently, should be administered to maintain the blood count within normal limits. Overdosage may cause jaundice, pyrexia, melæna and severe anæmia.

Acetylphenylhydrazine is a less toxic preparation than the above. It is given in capsules, in doses of 0·1 gm. daily, by mouth, for 7 to 10 days, followed by a rest period of two weeks. A second course may be administered if necessary.

ANTIBIOTICS AND ANTIBACTERIAL CHEMOTHERAPEUTIC SUBSTANCES

Modern Theories of Chemotherapy.

CHEMOTHERAPY, as a science, is evolving from long research to correlate the physiological actions of drugs with their chemical constitution. A great deal of knowledge is accumulating regarding the mechanism of the growth of cells, and of the influence of chemical groupings on vital processes, and to-day the organic chemist finds it progressively less difficult to synthesise a compound which will exert a specific physiological effect. When the effect produced is obviously due to a definite chemical structure, we have the fundamental conception of a chemotherapeutic substance. If a definite type of structure is capable of combating a bacterial or protozoal infection by interference with the physiology of the invading organism, the parent substance is termed a chemotherapeutic antibacterial or antiprotozoal compound. The term antibiotic is applied to antibacterial substances obtained from fungi and bacteria. In the following account of the mode of action of antibacterial chemotherapeutic substances, emphasis has been laid on the sulphonamides because, firstly, a great deal is known about the way in which they act, secondly, because of their intrinsic importance, and thirdly, because of their important influence on chemotherapeutic research. The introductory remarks in the chapter on Antiseptics and Disinfectants should also be consulted.

The Growth of Micro-Organisms.

Micro-organisms develop and multiply partly by the synthesis of simpler compounds into some new bacterial substance. Thus, given ammonia and carbon dioxide, *Bacterium coli* can synthesise protein, provided it can obtain the *energy* necessary for the process by the convenient presence of a combustible substance like dextrose. This particular synthesis appears to be brought about by a sequence of chemical changes, each, in all probability, the result of separate enzyme action. The new substance produced at each stage is termed an *essential metabolite*. In the case of the organism named, an early result of its activity is the production of amino-acids. By contrast, however, the development of *Bacterium typhosum* requires the initial presence of amino-acids in the nutrient medium. Amino-acids represent a stage in the synthesis of protein which the latter organism cannot itself achieve, and the term *growth-factor* is applied to amino-acids in relation to *B. typhosum*. In general, it will be apparent that **a growth factor for any given organism is simply an essential metabolite which the organism itself cannot synthesise.** So far we have considered only the elaboration of the actual bacterial cell. Provision must be made, however, for other processes subsidiary to growth, and *particularly for the liberation of energy*. Reference has already been made to the combustion of dextrose to this end. Such combustion, it is now known, requires the presence of a co-enzyme termed co-zymase, a chemical entity containing the nicotinic-acid complex. Co-zymase is an essential metabolite for all organisms; some, such as *Bacterium coli*, can synthesise it, but to others (e.g. *H. influenzæ*) it must be supplied as a growth factor. A few organisms, including the staphylococci and *B. proteus*, can synthesise co-zymase if they are provided with its nicotinic-acid fraction, and in these cases nicotinic acid is obviously a growth factor for the organisms named. Consideration of the foregoing helps to an understanding of the way in which certain antiseptics and chemotherapeutic agents may work. It has been fairly well demonstrated that substances which inhibit bacterial proliferation do so by interfering with an essential metabolite; in short, the organisms are starved. This interference can be of a varied character, namely:

(1) OXIDATION.—An oxidant in sufficient concentration in the medium will inhibit the growth of anærobes. The mechanism is to prevent the reduction of an essential metabolite which would normally be reduced in order that the associated enzyme may function. If the oxidising agent is a diffusible one, such as methylthionine chloride (methylene blue), it can also inhibit the growth of ærobes by diffusing into the *interior* of the bacterial cell, where conditions are anærobic, so that the drug can act as above.

(2) Some antibacterial substances, for example the mercuric ion, after penetration of the bacterial cell combine with an essential metabolite to form a compound which the organism is unable to utilise. It is suggested that penicillin combines with sulphydryl groups of bacterial cells which are essential for their growth.

(3) Some groups of compounds, of which the sulphonamides are a pre-eminent example, *compete* with an essential metabolite for the associated enzyme. The growth of the bacterium suffers accordingly. A number of essential metabolites whose physiological functions can be interrupted in this way are now known. In all cases the antibacterial compounds have a similar chemical structure to the essential metabolite, and so are able to link up with the enzyme concerned. At the same time they are sufficiently different from the essential metabolite to be devoid of metabolic utility. In the case of the sulphonamides, the essential metabolite inhibited is considered to be *p*-aminobenzoic acid. It was first discovered that extracts from streptococci, and also from yeast, could antagonise the action of sulphanilamide: *p*-aminobenzoic acid was then shown to be the chemical compound present in yeast which effected this antagonism. Since the inactivation does not partake of the nature of a chemical change, involving the formation of inert reaction products, it is assumed that *p*-aminobenzoic acid is an essential metabolite. The important therapeutic significance of this action is, of course, that it is *reversible*. A sufficient concentration of a sulphonamide, on account of its not grossly dissimilar structure, can take the place of *p*-aminobenzoic acid in connection with enzyme activity, and so disrupt the normal metabolic processes of the bacteria.

The **essential metabolite** which can be adsorbed and metabolised by the enzyme is the *specific substrate* of the enzyme, while the chemically related compound or *analogue*, which, although able to link up with the enzyme, cannot be metabolised, is termed the **inhibitor.** Other examples of this type of biological competitive action are: androgens and œstrogens, physostigmine and acetylcholine, carbon monoxide and oxygen (competing for hæmoglobin) and certain vitamins with their analogues. Some of these actions are mentioned elsewhere in the text.

The Clinical Evidence.

These general conceptions, outlined above, fit neatly the observed clinical facts. Thus, there is obviously need for sulphonamide to reach as quickly as possible an effective concentration in the infected tissue before the invading organism has had time to proliferate too freely, since the enzyme system has a greater affinity for *p*-aminobenzoic acid than for the sulphonamide. Again, in connection with the local application of a sulphonamide as, for example, to prevent gas-gangrene or suppuration, the application will prevent infection from developing, but has very little beneficial effect on tissues already heavily infected. Since damaged and infected tissues contain substances related to *p*-aminobenzoic acid, it follows that excess of the remedial drug must be applied to overcome the antisulphonamide substances. Some local anæsthetics, such as procaine, contain the *p*-aminobenzoic acid complex and can antagonise sulphonamides if used with the latter. Some bacteria normally susceptible to the action of sulphonamide may develop a resistance to the drug, particularly during the course of therapy. This "drug-fastness" is almost certainly due to the infective organism becoming nutritionally trained to synthesise the large quantities of essential metabolite necessary to inhibit the antibacterial agent. Finally, it must be noted that *p*-aminobenzoic acid is required by the tissues of the host, and that toxic symptoms produced by the sulphonamides are due, in part at least, to interference with normal metabolism of the patient undergoing treatment by the inhibition of essential metabolites. The sulphonamides are essentially bacteriostatic; they interfere with the proliferation of bacteria, but do not kill them (see below). But, this accomplished, the natural immunity-conferring bodies of the host can readily effect the destruction of the damaged and numerically few invading organisms.

The Sulphonamides

Chemically a sulphonamide is the amide of a sulphonic acid. Sulphanilamide (para-aminobenzenesulphonamide) is the simplest member of the group and modifications in its structures have led to the production of more potent compounds, acetylation of the sulphonamide group producing sulphacetamide, while substitution with the pyridine, thiazole, pyrimidine and dimethyl pyrimidine radicals give sulphapyridine, sulphathiazole, sulphadiazine and sulphamethyl pyrimidine respectively. Replacing the amido group by guanidine yields sulphaguanidine. These compounds are white crystalline powders, sparingly soluble in water, but more so in the presence of alkalis. Their sodium salts are readily soluble. They may be heated to 140° C. without dissociation. In solution some ionic dissociation occurs, the compounds behaving like weak acids, and activity depends mainly on the anion. Activity is enhanced in alkali solution since ionic dissociation is then more marked.

The mode of action of the sulphonamides has already been discussed. Their action is mainly bacteriostatic, but there is some evidence of a bactericidal effect. Differences in the action of the various compounds depend upon: (1) **Degree of ionic dissociation in the body fluids.** Thus sulphathiazole, more readily dissociated, is much more active than the much less dissociated sulphanilamide. It is also due to this factor that compounds like the former are much more effective against less susceptible bacteria such as staphylococci and pneumococci. (2) **Differences in rates of absorption and excretion** affect the concentration in the blood of the various compounds and may help to determine the type of condition for which a particular one may prove most suitable. Most of the sulphonamides, except sulphaguanidine, succinyl sulphathiazole and phthalyl sulphathiazole, are readily absorbed from the small intestine and to a slight extent from the colon. Sulphapyridine is absorbed more slowly and less completely than the other compounds given for their systemic effect. Sulphaguanidine is absorbed to the extent of about 50% only, whilst succinyl sulphathiazole and phthalyl sulphathiazole are hardly absorbed at all. It is for this reason that the latter group are given for their antibacterial effect in the gut. Sulphadiazine and its derivatives, sulphamezathine and sulphamerazine, are excreted slowly as compared with sulphanilamide and sulphathiazole so that high blood concentrations are more easily attained and maintained with the former drugs. (3) **Rates of diffusion** of the different compounds into the tissues vary, depending upon the degree to which each is bound to plasma proteins. Thus sulphanilamide is little bound and diffuses rapidly and fairly equally into most secretions, C.S.F., pleural and synovial fluids, and fœtal circulation, giving rise to concentrations about the same as in blood, whereas with sulphathiazole, which diffuses to a much less extent, the concentration, *e.g.* in the C.S.F., is only about half that in the blood. Sulphapyridine and sulphathiazole are intermediate in their rates of diffusion.

Only small amounts of the drugs are excreted in the milk. Sulphapyridine accumulates in the liver in higher concentration than in the blood. Sulphonamides are detoxicated in the liver by acetylation of the *p*-amino group, acetylation being more marked with sulphanilamide and sulphapyridine than with sulphathiazole and sulphadiazine. About 20% of the compound is acetylated and is excreted in the urine together with the parent substance. These N_4 acetylated derivatives are therapeutically inert and, being generally less soluble than the original substance, tend to crystallise in the kidneys and so block the tubules. This danger is greater with the less soluble compounds like sulphapyridine and sulphadiazine. The risk of drug-fastness (see above) due to the survival of bacteria which develop into drug-resistant strains can be reduced by refraining from giving the drug in small doses over a long period, an exception being the use of sulphonamides in prophylaxis (see below), in which the number of bacteria to be overcome is small. Furthermore, organisms resistant to a weaker sulphonamide like sulphanilamide may still be susceptible to a more potent one like sulphathiazole or sulphadiazine. Sulphonamides act best when the body temperature is raised in fever. Reference has already been made in the previous section as to ensuring that an adequate concentration of the drug is reached in the early stages of an infection before the invading organisms are too numerous and before suppuration has occurred, because bacteria and tissue autolysates contain *p*-aminobenzoic acid or related substances opposing the action of sulphonamides. It is important, therefore, to use a large initial dose of the drug and in severe infections to give it parenterally as the sodium salt. Nevertheless the effectiveness of sulphonamides does not increase in direct proportion to increasing dosage, but lags behind it. Where pus and necrotic tissue are present this cannot be sterilised by the drug, and surgical drainage, etc., is necessary. In order to maintain an effective concentration of the drug throughout the 24 hours, 4-hourly administration throughout the period is necessary, although the slower rate of excretion of sulphamezathine and sulphamerazine enables 6-hourly dosage to be used effectively.

Dosage: This will depend upon: (1) The severity of the infection, a higher concentration of the drug being necessary to deal with severe infections. Chronic infections do not require the initial large dose. (2) The sensitivity of the drug of the organisms causing the infection. Thus, some organisms such as staphylococci may be naturally resistant to sulphonamides. Other bacteria, like streptococci, which are normally susceptible to these drugs may have naturally resistant strains or may develop acquired resistance. In all these groups higher dosage is required and more potent sulphonamides such as sulphathiazole or one of the sulphadiazine group should be used, or penicillin employed in suitable cases. In cases not responding well after 3 or 4 days, the sensitivity of the causal organisms to sulphonamides can be tested *in vitro.* Blood concentrations of the drugs with therapeutic dosage vary from 2 to 15 mg. per 100 ml., depending upon the size of the dose, the time at which the blood is collected in relation to the previous dose and the type of sulphonamide used, the slowly excreted sulphadiazine group giving higher blood levels. Infections which are severe or due to relatively resistant organisms require blood levels of approximately 10 mg. per 100 mil., whilst for milder infections about 5 mg. per 100 mil. suffice. An estimation of the blood level may be useful in assessing further dosage in cases not responding well. (3) Children require smaller doses, but in proportion to their weight tolerate sulphonamides better than adults. The drugs should be continued for 2 or 3 days after the pyrexia has subsided, but treatment beyond a week is not usually necessary. Urinary infections require smaller doses because of the considerable concentration of the drug in the urine. For oral administration, which is the routine method, the 0·5 gm. tablets are preferably crushed and given with water, or better still with an alkali mixture of 30 gr. each of sodium bicarbonate and sodium citrate in 1 oz. of water, the alkali increasing the solubility, reducing any tendency to vomit, increasing the absorption of the drug, and by making the urine alkaline, diminishing the risk of crystallisation in the tubules and increasing the activity of the drug in urinary infections. For severe infections, in comatose cases or where the patient is unable to tolerate the drug orally, the soluble sodium salts of sulphapyridine, sulphathiazole and the sulphadiazine group are available in ampoules containing 1 gram of the drug for parenteral administration. As the sodium salts are alkaline and may cause tissue necrosis at the site of injection, they are best given intravenously either as a single injection or by continuous drip transfusion in saline (not blood or plasma). They are sometimes given deeply into the *vastus externus* muscle so as to avoid damage to the sciatic nerve with permanent paralysis. With the exception of soluthiazole, intramuscular injections are painful. The following scheme of dosage is suitable for systemic therapy: (1) *For severe infections.*—Initial dose of 2–4 gm. intravenously plus 1·5 gm. orally, followed by 1·5 gm. orally 4-hourly for 2 to 3 days, and then 1 gm. 4-hourly. (2) *For moderate infections.*—Initial dose 2 gm. orally, followed by 1 gm. orally 4-hourly for 4 days and then 0·5 gm.

4-hourly. For children the following table gives a suitable scheme of dosage:

Up to 1 year	..	0·5 gm.	initially followed by	0·25 gm. 4-hourly.
1 to 3 years	..	0·5 gm.	,, ,, ,,	0·5 gm. 4-hourly.
4 to 10 years	..	0·75 gm.	,, ,, ,,	0·75 gm. 4-hourly.
11 to 15 years	..	1·0 gm.	,, ,, ,,	1·0 gm. 4-hourly.

In severe infections of childhood the following intravenous dose should be given in addition to the initial oral dose: 0·5 gm. (1 to 3 years), 1·0 gm. (4 to 10 years), 1 to 2 gm. (11 to 15 years).

In the case of sulphamezathine and sulphamerazine, 6-hourly administration is effective. For dosage of sulphaguanidine, succinyl sulphathiazole and phthalyl sulphathiazole see below. All patients on sulphonamides require copious fluids to minimise risk of crystalline deposits in the kidneys.

THERAPEUTIC INDICATIONS.—Numerous organisms are susceptible to sulphonamides. Nevertheless in many infections previously treated with sulphonamides, penicillin has proved more effective and should be employed where available. Penicillin, however, requires to be injected, and some organisms such as *B. coli* and the dysentery group respond very much better to sulphonamide therapy, which may also prove effective where organisms have become resistant to penicillin. Sulphonamides do not neutralise toxins, so that antitoxins should be used as well when indicated, and additional measures such as blood transfusion and surgical therapy employed where necessary. Sulphonamide therapy is of value in the following conditions:

(1) *Hæmolytic streptococcal infections* such as septicæmia, erysipelas, puerperal sepsis, pneumonia, acute tonsillitis, otitis media, mastoiditis, septic complications of scarlet fever, meningitis, infected wounds, cellulitis, etc. Penicillin is to be preferred or given with sulphonamides in severe infections. (2) *Meningococcal septicæmia and meningitis.*—Severe cases should receive penicillin in addition to sulphamides. (3) *Pneumococcal infections*, particularly pneumonia and pneumococcal peritonitis. The sulphadiazine group are most suitable and sulphanilamide is ineffective. Infections which are severe or not responding, or if meningitis is present, require penicillin. (4) *Gonococcal infections* (gonorrhœa, ophthalmia neonatorum).—Penicillin is to be preferred because of the short duration of treatment required. (5) *Staphylococcal infections.*—Penicillin is the drug of choice and is essential if the infection is severe. Sulphathiazole or sulphadiazine may be used in addition to penicillin or if the latter is not available. (6) *Urinary infections* (cystitis, pyelitis, etc.) due to *B. coli* and hæmolytic streptococci respond well to sulphanilamide, sulphacetamide, sulphamezathine, and these compounds are suitable because their solubility minimises renal damage. More resistant bacteria, e.g. *B. proteus*, require sulphathiazole or sulphadiazine. Mandelic acid should be given in sulphonamide-resistant infections. The efficacy of sulphonamides is reduced by urinary obstruction (calculi, pregnancy, etc.). The presence of renal impairment necessitates smaller doses because of faulty drug excretion. (7) *Burns and wounds.*—Prophylactic therapy with sulphonamides applied topically has proved of value in limiting infection, although when the latter has occurred systemic therapy is required. Penicillin has largely supplanted sulphonamides in these conditions, par-

ticularly as it is much more effective in staphylococcal and gas-gangrene anærobic infections. Sulphanilamide, because of its solubility, is suitable for local application and may be used as a powder for wounds. Other suitable powders are 1 part of sulphanilamide and 3 parts of sulphathiazole, or 1 part of proflavine and 99 parts of sulphathiazole (see also Flavazole). The latter is more slowly absorbed from the wound. A cream is the most suitable preparation for the treatment of burns. (8) *Peritonitis and perforating abdominal wounds.*—Suspensions of sulphadiazine 15 gm. in 60 mil. of saline with 3% pure gelatine added may be inserted into the peritoneal cavity. Suspensions of sulphanilamide, phthalyl sulphathiazole or succinyl sulphathiazole have also been used. (9) *Skin diseases.*—Impetigo, erysipelas, erysipeloid, infected eczema, dermatitis herpetiformis, erythema multiforme, echthyma, cutaneous Leishmaniasis. *Local* application may result in drug sensitivity with the occurrence of an intractable dermatitis and marked reaction to sunlight. It may prevent sulphonamides from being subsequently used for a severe infection. Impetigo responds well to other measures and should not require sulphonamides. *Systemic* therapy with the latter is effective in many of the other conditions enumerated above. The best preparations for local application are 5% sulphathiazole or sulphadiazine in zinc paste, which should be applied for no longer than 5 days to reduce the danger of sensitisation. (10) *Eye diseases.*—Blepharitis, conjunctivitis. Sulphacetamide locally is the best sulphonamide, but penicillin is more effective. (11) *Actinomycosis.*—Penicillin is preferable. (12) *Plague and tropical pyomyositis.* (13) *Lymphogranuloma inguinale* and trachoma are the only virus infections in which sulphonamides are effective, although these may be given to counteract the secondary invaders in smallpox, influenza and measles. (14) *Intestinal diseases.*—Sulphonamides have proved of value in the treatment of dysentery, particularly Flexner infections. Shiga dysentery responds to maximum dosage. Cholera is said to be benefited by sulphaguanidine. Indefinite results have been obtained in ulcerative colitis and infantile gastro-enteritis. The preparations commonly employed are sulphaguanidine, succinyl sulphathiazole and phthalyl sulphathiazole, although there is evidence that sulphadiazine is the drug of choice in dysentery. Sonne carriers, difficult to treat, have responded to therapy with sulphanilyl benzamide and sulphanilyl amidobenzamide. The value of sulphonamides in anthrax is uncertain and penicillin is much more effective. *Streptococcus viridans* and most strains of non-hæmolytic streptococci are insensitive to sulphonamides but may respond to penicillin. Sulphonamides are of no value in tuberculosis. Bacterial endocarditis must be treated with penicillin.

PROPHYLACTIC ADMINISTRATION.—Sulphonamides in small doses have been used for prophylaxis in several conditions to be enumerated. The danger of toxic reactions is not great in view of the small doses employed, but may appear particularly between the 1st and 4th weeks. Sensitisation may make subsequent administration of the drug for a severe infection difficult and, furthermore, sulphonamide-resistant bacteria may develop, but these events are rare with prophylactic therapy. Individuals in semi-closed communities, *e.g.* barracks, during an outbreak of meningococcal meningitis, have received sulphonamides in doses of 2 gm. daily for 3 days, and this has cured carriers and brought the epidemic to an end. Outbreaks of streptococcal infection, *e.g.* tonsillitis, scarlet fever, can be controlled by giving 1 gm. daily for 10 days. The administration of 0·5 to 1 gm. daily during the winter months to cases of rheumatic fever, *i.e.* (1) children or (2) adults with recurrent attacks of rheumatic carditis, reduces the incidence of streptococcal throat infections and the risk of subsequent rheumatic attacks. The leucocyte count must be watched, particularly between the 2nd and 6th week. Prophylactic therapy is also used in the prevention of urinary infections after cystostomy.

TOXIC EFFECTS.—Malaise and depression are least marked with the sulphadiazine group. Vomiting, most marked with sulphapyridine and least with the sulphadiazine group, can be lessened by giving the drug as recommended above under oral administration. Cyanosis due to methæmoglobinæmia and sulphahæmoglobinæmia is most common with sulphanilamide and rare with the other compounds. It is of importance only in anæmic patients and is rarely an indication for stopping therapy, although a change may be made to one of the other compounds. Watery purgation should be avoided, but there is no need to omit sulphur-containing foods. Hypersensitivity [1] may appear either during a first course of therapy, commonly about the 7th to 9th day, or very soon after beginning a second course of the drug. Sensitivity following local application for skin diseases has been referred to above. Hypersensitivity may result in any combination of the following symptoms: (1) Rashes (rubellar, morbilliform, scarletiniform and, in the case of sulphathiazole, like erythema nodosum) which itch a great deal. Exposure to sunlight should be avoided because of photosensitivity. (2) Drug fever, which may be associated with rigors, delirium, prostration and albuminuria. It subsides rapidly, when the drug is stopped, an important difference in distinguishing it from pyrexia due to the causal infection. In a few cases where the drug has been continued in the presence of hypersensitivity, death in coma has resulted, focal visceral necrosis occurring. When symptoms appear, the drug must be stopped and copious fluids given to aid drug excretion. The incidence of sensitisation can be reduced by not giving the drug for longer than a week. It is due to a combination of sulphanamide and body protein and in many cases appears to be specific to the particular sulphonamide used. It can be tested for by the intradermal injection of the sulphonamide plus serum, and if the test is positive a change should be made to a different sulphonamide or, better still, to penicillin. Desensitisation is achieved by giving small doses orally, *e.g.* 0·1 gm. 4-hourly for a week. Leucopenia is common and, unless the total count falls below 4,000 or the polymorphs below 50%, need not lead to the drug being stopped. Agranulocytosis, often with severe throat infection, is serious and is generally regarded as a hypersensitivity phenomenon; it is most likely to occur with prolonged therapy. The drug must be stopped and copious fluids, transfusions, sodium pentose nucleotide and pyridoxin given. Its prevention lies in having twice-weekly blood counts done if the drug is given for longer than a week, except in prophylaxis therapy. Mild anæmia is common and curable by iron. Aplastic anæmia, purpura and acute hæmolytic anæmia are rare and serious. Hæmaturia, severe oligouria and anuria may result from drug crystallisation in the kidneys, and occasionally death from uræmia may occur. Renal complications are much more likely to occur with sulphapyridine, sulphathiazole and sulphadiazine. Alkalis and copious fluids diminish the risk by increasing the solubility of the drug and its acetyl derivative. Frequent urine testing, measurement of output and microscopy for crystals are necessary. If symptoms appear the drug must be stopped, but copious intravenous fluids must not be given if the patient has anuria, otherwise œdema of the lungs may result. Heat to the loins may be tried, but if severe oliguria persists for 24 hours or anuria for 12 hours, cytoscopy and ureteral catheterisation must be done and the renal pelvis washed out with 2% sodium bicarbonate solution. If this fails pyelostomy is necessary. Other complications are mental confusion, visual disturbances, vertigo, acidosis and, rarely, peripheral neuritis and hepatitis with jaundice.

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[1] A syndrome resembling *polyarteritis nodosa* may occur as an unusual complication in therapy with sulphonamides, arsenicals and thiouracil.

In the description of the individual sulphonamides which follows, in order to avoid repetition, only points not covered by the previous sections will be mentioned in any detail, and the reader must refer back for information on the pharmacology, therapeutic uses and toxic reactions of the drug.

Sulphanilamide (*p*-aminobenzenesulphonamide).

This is one of the least active of the sulphonamides and is ineffective against pneumococci and staphylococci. Its solubility makes it suitable for local application (see above). It is more likely to produce cyanosis, and has to a large extent been replaced by the less toxic and more potent sulphadiazine derivatives. A saturated solution, 0·8% in normal saline, may be given intravenously, or Soluseptasine or Sulphanilamide E.O.S. are suitable soluble preparations.

Sulphacetamide (*p*-aminobenzene sulphonacetamide) (*Albucid**).

This is an acetyl derivative of sulphanilamide which is therapeutically active. About 60% of the intake is excreted as sulphanilamide and the remainder as the inert N_4 acetyl derivative of sulphanilamide. It is a useful compound in urinary infections and, because in aqueous solution it is neutral to litmus, a 2·5 to 20% solution is used in the treatment of conjunctivitis and infected corneal ulcers, whilst a 2·5 to 10% ointment is employed for blepharitis.

Sulphapyridine. 2-(*p*-aminobenzene sulphonamido)pyridine (*Dagenan**).

This drug is of historical interest in the treatment of pneumonia, etc., but its toxicity has resulted in its being largely supplanted by sulphadiazine and its derivatives.

Sulphathiazole. 2-(*p*-aminobenzene sulphonamido)thiazole (*Cibazol,* Thiazamide**).

This is one of the most active of the sulphonamides and was used a great deal in staphylococcal infections before the advent of penicillin. It is rapidly excreted and effective blood levels may be difficult to maintain. It is still employed fairly commonly when sulphonamide therapy is indicated. For local applications see above. It is more toxic than the sulphadiazine derivatives. A sodium salt is available for intravenous medication.

*Soluthiazole.**

This is the disodium cinnamylidene dibisulphite derivative of sulphathiazole. It is readily soluble in water, and the solution having a pH of about 7 is therefore free from the irritant effects on the tissues produced by the strongly alkaline sodium salts of sulphathiazole, sulphadiazine, etc. It can thus be injected by any route and absorption is rapid and effective. One gramme contains 0·44 gm. of sulphathiazole. Very little of the drug is conjugated because of rapid elimination. Toxicity and urinary crystallisation is less than with sulphathiazole and its sodium salt. It is a useful drug for initiating sulphonamide therapy and for comatose or vomiting patients. It is less active against staphylococcal infections than sulphathiazole, and the dose should be modified accordingly.

Sulphadiazine (sulphanilamido-pyrimidine).

This is an effective and commonly used drug, particularly in pneumococcal infections. It is, however, more likely to produce hæmaturia and anuria than its derivatives and these are preferred for this reason. For local applications see above. A sodium salt is available for intravenous therapy.

Sulphamezathine (sulphanilamido-dimethylpyrimidine).

This dimethyl derivative of sulphadiazine is one of the least toxic of the sulphonamides, urinary complications being rare, vomiting unusual and agranulocytosis not yet described, and it is, in addition, a very effective compound. In view of its slow excretion it is often prescribed 6-hourly. A soluble sodium salt is available.

Sulphamerazine (sulphanilamido-methylpyrimidine).

This methyl derivative of sulphadiazine has properties and advantages very similar to sulphamezathine. It is claimed to be as effective as sulphadiazine in half the usual dosage of the latter. Its slow excretion makes 6- or 8-hourly dosage effective, and in children the makers recommend 12-hourly dosage.

*Sulphatriad.**

This combination has been introduced to minimise crystalline deposition of sulphonamides in the urine, and so to reduce the possibility of renal damage. It is a mixture of sulphathiazole 0·37 gm., sulphadiazine 0·37 gm., and sulphamerazine 0·26 gm. per gram. It is as effective therapeutically as the individual sulphonamides of the mixture, and has the same therapeutic indications and dosage. Its advantage lies in the fact that the solubility of each constituent is not directly affected by the presence of the others, and since the concentration of each constituent is only about one-third of what it would be if it had been present as a single compound, deposition of crystals is minimised. This is particularly useful in elderly patients.

Sulphaguanidine (sulphanilyl-guanidine).

Administered by mouth it produces a high concentration in the fæces, since only about 50% of the drug is absorbed, although the latter makes toxic symptoms possible. High dosage (3 to 5 gm. four times daily) can be given and provides effective medication in dysentery due to Flexner and Shiga infections, but Sonne organisms are more resistant. The drug is also of value for the disinfectation of dysentery carriers. Sulphaguanidine has also been used to treat ulcerative colitis, but results from oral medication are, on the whole, disappointing and better results have been reported from the administration of retention enemata, consisting of 5 gm. of the powdered drug suspended in mucilage.

Succinyl Sulphathiazole (*Sulfasuxidine**).

Administered by mouth this derivative of sulphathiazole is only very slightly absorbed, an average of 5% being excreted by the kidneys. In oral doses of 2 gm. 5 times daily, or 0·25 gm. per kilo, it has a marked antibacterial action on bowel organisms, particularly on the coliform flora. It is effective against the Flexner, Shiga and, to a less extent, Sonne strains of dysentery bacteria, and markedly inhibits proteolytic bacteria. The drug has been found useful for pre-operative preparation and post-operative treatment in cases of surgery of the intestinal tract. It has been employed also as a surface antiseptic.

Phthalyl Sulphathiazole (*Sulfathalidine,* Thalistatyl**).

This drug is claimed to be more effective than succinyl sulphathiazole and has similar indications for therapy. The dose recommended in dysentery is 0·04 gm. per kilo every 4 hours for 12 doses, and then 0·02 gm. per kilo 4-hourly for a total of 7 days.

Patients receiving the last three compounds for more than a few days should be given supplementary vitamin B preparations.

Maphenide (*Marfanil*) (4-Aminomethylbenzenesulphonamide).

This German compound is freely soluble in water and has the advantage of not being inhibited by *p*-aminobenzoic acid or pus, and of being particularly effective against the clostridia of gas gangrene as well as against sulphonamide-resistant strains of streptococci. It is said to be useful for local application to wounds, but its value is otherwise limited. A similar and more recent compound is V 187 (*p*-methylsulphonylbenzamidine hydrochloride).

Sulphones.

Promin belongs to the group of sulphones and has an antibacterial action against the tubercle and leprosy bacilli. Beneficial results have been reported from local application of the drug to superficial tuberculous lesions and also to patients with leprosy, but results in pulmonary tuberculosis have not been very promising, particularly as it causes anæmia. More potent and less toxic sulphones are **Promizole,** a thiazole derivative of promin, and **Diasone.** The dose of the latter for leprosy is 5 to 14 gr. daily by mouth, the dosage being gradually increased so that the maximum dose is being taken after three or four weeks. *Promanide** as a 5% jelly or ointment can be applied locally to lupus vulgaris and superficial tuberculous lesions.

Para-aminobenzoic acid.

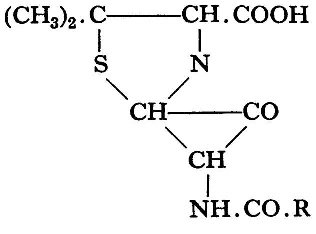
This substance is a member of the vitamin B complex and has been found of value, both experimentally and clinically, in Rickettsial infections such as louse-borne and scrub typhus. The dosage recommended is 8 gm. initially followed by 2 to 3 gm. 3-hourly, given orally. Ten mil. of 5% sodium bicarbonate is given with each dose of the drug so as to allay gastric irritation. It is desirable to maintain a drug blood level of 10–20 mg. per 100 mil. in louse-borne typhus, and 30–60 mg. per 100 mil. in scrub typhus. A fall in leucocytes may occur and blood counts are necessary. There may be mild delirium with large doses. Its use in premature greying of the hair is based on experimental evidence.

Antibiotics

Penicillin.

Penicillin, the most potent of all known antibiotics, is produced by the mould, *Penicillium notatum.* It was discovered by Fleming in 1929 and a crude preparation obtained by Florey and his co-workers in 1938. The commercial preparation involves the large-scale culture of *P. notatum* on a fluid medium from which penicillin is extracted either (1) by alternate transference in organic solvents and dilute alkali, or (2) by adsorption on activated charcoal. The solution is then sterilised by Seitz filtration and freeze dried *in vacuo.* It is claimed that the strain of the mould can be improved and a higher yield of penicillin obtained by (1) exposing the mould to irradiation by X-rays or U.V.L., or to the action of colchicine which induces autopolyploidy whereby strains are produced whose cells have an increased number of chromosomes and give higher yields of penicillin. Some workers have not confirmed this. (2) By using *P. chrisogenum* instead of *P. notatum.*

Chemistry.—Penicillin is a strong monobasic acid, forming sodium, calcium and other salts. Five different forms have been isolated in the crystalline state, the first four being termed I (F), II (G), III (X), IV (K), the numbers being the English and the letters the American designations. They are dipeptides, made up of 2 amino-acids, dimethyl cysteine and an acetylated serine, the alcoholic group of which has been oxidised to the aldehyde. This peptide structure is incorporated into a four-membered β lactam ring, this being responsible for the properties of the drug. The formula is given below. Very small amounts of penicillin I and II have been synthesised. The side chain "R" in the formula varies in the different penicillins, being 2-pentenyl for I, benzyl for II, *p*-hydroxybenzyl for III and *n*-heptyl for IV. The β lactam ring is readily fissured by alkalis, primary alcohols and amines, thiol compounds like cysteine, and the enzyme penicillinase, resulting in the production of penicilloic acids and accounting for the instability of the drug in the presence of these reagents. With mercuric chloride, penicilloic acids are broken down into penicillamine (dimethyl cysteine) and penaldic acids. Penicillin is hydrolysed by weak acids, forming isomeric penillic acids. Methyl and benzyl esters have anti-bacterial activity in some animals because they are hydrolysed *in vivo,* but not so in man because the hydrolysing enzyme is absent. Penicillin



used as the sodium or calcium salt is generally supplied in an impure state with an activity of 300–1500 units per mg. and is a yellowish to brown powder, the sodium salt readily soluble in water. Pure crystalline sodium penicillin II is a white powder with an activity of 1,600 units per mg.

Stability.—The drug deteriorates in the presence of moisture and, as the salts are hygroscopic, moisture must be excluded when storing the solids which need not then be placed in a refrigerator. Aqueous solutions are gradually hydrolysed and so progressively inactivated into penicilloic acid. Factors further increasing hydrolysis and inactivation of solutions are: (1) Deviation of the pH from the stable range pH_5–pH_7 (maximal stability pH_6): acids particularly cause deterioration. (2) Increasing the temperature of the solution, which is therefore best stored in a refrigerator. Addition of phosphate buffer increases the stability of solutions which may then be boiled with only small loss of activity. (3) Increasing the purity of the drug, impure forms being more stable because of the buffering effect of the impurities. (4) Concentrated solutions, which undergo more hydrolysis, are less stable than dilute ones. (5) Penicillinase, an enzyme produced by some bacteria such as *B. coli* and some airborne organisms. (6) Chemicals such as glycerin, heavy metals, cysteine, thiomersalate, chlorbutol, and oxidising agents. Concentrated alcohols also reduce its activity, but rubber caps of bottles containing the drug may be sterilised with alcohol before injection. (7) Synthetic rubber. The addition of phosphate buffer to the solution will reduce the inactivating effects of synthetic rubber. Penicillin II appears to be the most stable form.

Standard Units.—(1) The *Oxford Unit* is the original unit and one definition of it is the amount of penicillin dissolved in 50 ml. of broth which will just inhibit a test strain of staphylococcus. It is used in the estimation of penicillin levels in body fluids. One mega-unit = 1 million Oxford units. (2) The *International Unit* is defined as the specific activity contained in 0·6 microgram of the international standard. It is approximately equivalent to the Oxford unit. (3) The *British National Standard.* The activity contained in 0·625 microgram of this standard is equivalent to 1 international unit.

Pharmacology.—Penicillin is bacteriostatic at lower and bactericidal at higher concentrations. It interferes with early bacterial development, inhibiting enzymatic action concerned with nucleotide metabolism and suppressing bacterial respiration. These effects are possibly due to the reaction of the β lactam ring of penicillin with the sulphydryl groups in the bacterial cells essential to their growth. Whilst it has some bacterial action in the early "lag" phase of growth of a bacterial culture, it is during the next phase of rapid logarithmic growth that its bactericidal and bacteriolytic actions are most marked, whilst it has little action in the final resting phase. When penicillin acts on a susceptible strain of organism a few of the bacteria, termed persisters, escape destruction because they are temporarily in a resting phase. Low temperatures and sulphonamides which inhibit bacterial cell division may thus reduce the bactericidal action of the drug. This action is enhanced by (1) raising the temperature up to a point; (2) reducing the pH, the drug being twice as active at pH 6·5 as at 7·5.

Penicillin has the following advantages as an antibacterial compound: (1) Practically non-toxic and so can be given in large doses. (2) Does not damage leucocytes or hinder tissue regeneration. (3) Not inhibited by blood, pus, other tissue fluids or tissue autolysates. (4) Wide range of activity against many types of bacteria. (5) Effective against susceptible bacteria in very high dilution. A satisfactory blood level of the drug for many infections is 0·1 unit per mil. (6) Action is little affected by number of organisms present. Penicillin IV, whilst more active *in vitro*, is less effective than II and III *in vivo* because it is more rapidly destroyed in the body. It is therefore desirable to keep as low as possible its proportion in commercial preparations. These, as a rule, contain a predominance of penicillin II. Penicillin III is more active than II. The drug is rapidly excreted, mainly in the urine but also to a small extent in the bile and saliva; some is destroyed in the body. Penicillin may induce premature menstruation and there may be some increased tendency to bleed after operation.

Toxicity.—This is slight and is due mainly to impurities and to the kations of the penicillin compound. Pain on injection is least marked with pure preparations, particularly if the buttocks are used as the site of injection, although massive doses produce discomfort as a result of their osmotic pressure. Thrombosis on intravenous injection may occur, particularly after large doses, and can be prevented by adding heparin, but penicillin may induce increased sensitivity to heparin. In experimental animals convulsions can be produced by injecting the drug into the cortex. Allergic reactions may occasionally follow a second course of the drug, the patient having been sensitised by a first course, resulting in urticaria, angeioneurotic œdema, cutaneous sensitivity to intradermal injection of the drug, and symptoms resembling serum sickness. Such sensitivity may follow local administration, *e.g.* eye drops. These allergic symptoms may be benefited by anti-histamine drugs. Desensitisation can be carried out by oral administration of increasing doses. In the treatment of syphilis penicillin may induce a Herxheimer reaction with a temporary exacerbation of symptoms which may necessitate a temporary reduction in dosage.

Methods of Administration and Dosage.—The drug must be brought into contact with the infecting organisms in adequate concentration for a sufficient length of time. It is rapidly absorbed when given by injection, applied to wounds or administered by inhalation. There are wide variations in the serum concentration of the drug following its injection. Average serum levels of ·2 units per mil. after 20,000 units and 1·7 units per mil. after 100,000 units are attained when the drug is given intramuscularly, a maximum level being reached within ½ hour and with the smaller dose falling below an adequate level in 2–4 hours. With continuous intravenous or intramuscular drip therapy it is easier to maintain a continuous adequate concentration of the drug in the blood. The larger the dose the longer will a satisfactory blood level be maintained. Renal disease impairing excretion will also maintain the blood level. Solutions used for injection must be free from pyrogens, be sterile and used soon after preparation. With no commercial shortage and with increasing cheapness of the drug the larger doses mentioned below are coming into greater favour, as they help to bring the infection under more rapid control and so lessen tissue damage and aid rapid healing. Relapses can be prevented by prolonging the course of therapy. As the drug is non-toxic, children and infants tolerate large doses, and these can be estimated on a basis of bodyweight, taking 140 lbs. as that of a typical adult.

Systemic Therapy.—(1) *Intravenous Therapy.*—Continuous intravenous drip is still used, 200,000 units to 500,000 units being given in 24 hours in 1 or 2 litres of normal saline or 5% dextrose. Large single doses, 200,000–500,000 units, with heparin, are not often used now. (2) *Intramuscular Therapy.*—(*a*) Continuous intramuscular drip, 100,000–500,000 units in ·1 to 1 litre of normal saline, is often used, but may produce sterile abscesses at the site of injection. Advantages are avoidance of frequent injections and, as compared with the intravenous drip, much smaller volumes of fluid are required. (*b*) Intramuscular injections, 20,000-50,000 units 3-hourly, the contents of the rubber-capped vial being dissolved in sterile water or normal saline. This is the most common method employed. In general practice, where it is usually difficult to give such frequent injections, large doses of 100,000 to 1 million units of a pure penicillin which can be dissolved in a few ml. of fluid are given twice daily. Although it is more difficult by this method to maintain adequate blood levels, it is satisfactory for any but very severe or very chronic infections, when 3-hourly dosage is required. In order to prolong the action of penicillin by decreasing the rate of its absorption and so reducing the frequency of injections the drug can be dissolved in 5% dextrose, or adrenaline 1 in 25,000 can be added. The most commonly employed method is the suspension of the drug in oil, a mixture of beeswax and arachis oil or ethyl oleate being used. The B.P. oily injection contains 125,000 units per mil. unless the prescriber specifies otherwise, and double this concentration is preferable. These oily suspensions produce prolonged soreness and their absorption is variable, high peak levels in the blood are difficult to obtain and the mixture is solid at room temperature. (3) *Intramedullary Drip* is sometimes used in osteomyelitis and where extensive burns make intramuscular injections impracticable. (4) *Oral Administration.*—As the drug is inactivated by gastric acid and irregularly absorbed from the alimentary tract, oral therapy is uncertain in its effect but aims at avoiding injections, especially in infants, and prolonging the action of the drug. Large doses, 50,000 to 100,000 units, aid the absorption of adequate amounts and this can be further assisted by giving the drug on an empty stomach and protecting it from gastric acid by giving it in doubly-coated enteric capsules and/or neutralising the gastric juice by giving alkalis (aluminium hydroxide gel, magnesium trisilicate or oxide) or the concurrent administration of sodium citrate[1]; these alkalis also adsorb the drug and release it more slowly. In infants, satisfactory results have been obtained by giving a saline solution of the drug in 1 oz. of the milk feed (100,000 units producing adequate blood levels for 15 hours in infants under 1 month, and for 6 hours in older infants).

Local Therapy.—It is often practicable to apply or administer penicillin at the site of infection and thus ensure an antibacterial concentration of the drug. Thus, depending upon the condition to be treated, the following methods are available: (1) *Into Serous or Abscess Cavities.*—In the case of infected serous cavities, *e.g.* empyema, the injection into the cavity of a large dose of penicillin, 100,000 to 200,000 units, after the pus has been aspirated will ensure adequate local concentrations and will also result in bacteriostatic blood levels being maintained for some hours as a result of delayed absorption of the drug. Very toxic cases require intramuscular injections in addition. (2) *Intrathecal.*—The drug does not penetrate the "blood brain barrier" into the C.S.F. to any extent, although such penetration is increased in meningitis. It is therefore necessary when treating infections of the brain, spinal cord and meninges, to give the drug intrathecally (10,000 to 20,000 units in 5 mil. normal saline daily), supplemented by systemic therapy. Pure penicillin should be employed if possible. (3) *Inhalation.*—In respiratory infections, 20,000 to 40,000 units per ml. 4-hourly may be given as a mist by inhalation from a suitable inhaler. The sputum and sometimes the blood will contain antibacterial quantities of the drug. (4) *Topical Therapy.*—The following preparations are employed: (*a*) Ointments and creams containing 500 to 1,000 units per gram for treatment of infected skin conditions, superficial wounds and abscess cavities, and burns. Eye ointments for eye infections. (*b*) Lotions containing 250 to 1,000 units per ml. normal saline or water, used as medicated dressings or compresses for skin infections, burns, abscesses and sinuses. (*c*) Drops, 2,500 units per ml. normal saline, for eyes, nose or ears. (*d*) Lamellæ, 100 to 250 units with lactose, for eye infections. (*e*) Powder, 2,500 to 5,000 units per gram, made up with sulphathiazole powder, dried serum or plasma, or lactose for application to wounds or as a snuff for nasal infections. The powder is either dusted on or applied by means of an insufflator. (*f*) Lozenges or pastilles, 500 units calcium penicillin per gram 2-hourly, for use in buccal infections. Lozenges are placed between gums and cheek and allowed to dissolve. Wafers for chewing contain 10,000 to 20,000 units. (*g*) Tablets of pure penicillin can also be inserted into wounds.

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[1] Tablets containing penicillin (20,000 units) and sodium citrate are available commercially.

Comparison with Sulphonamides.—Despite the advantages possessed by penicillin over the sulphonamides, namely its effectiveness in high dilution, its non-toxicity, its non-inhibition by pus, etc., and its not being affected by the number of bacteria present, the sulphonamides are more easily administered and in some infections, e.g. *B. coli* urinary infections, they are much more effective than penicillin. It is not certain to what extent there is a synergistic effect between penicillin and the sulphonamides as the bacteriostatic action of the latter may enhance that of penicillin in the early lag phase of bacterial growth, but may reduce the bactericidal action of penicillin in the logarithmic phase by depressing bacterial division. Nevertheless the concurrent administration of the two compounds may be an advantage in some infections (see below).

Acquired Resistance.—Whilst acquired bacterial resistance to penicillin is much less likely to occur than with the sulphonamides it may develop, particularly with inadequate dosage. Bacteria which have become penicillin-resistant *in vitro*, soon lose this power with succeeding generations of organisms and even the resistant bacteria may be killed by higher concentrations of the drug. Such drug resistance developing in a particular strain *in vivo* is due to the survival of the more resistant organisms and possibly to their acquiring the ability to produce penicillinase. Penicillin and sulphonamide resistance are not identical and strains which have become resistant to the one will still be susceptible to the other drug which should be used under these circumstances.

Therapy.—The following bacteria are susceptible to the therapeutic action of penicillin: *Staph. aureus, Staph. albus, Strep. hæmolyticus, Strep. viridans* (but not all strains), *Strep. anærobis, Dip. pneumoniæ, Neis. gonorrhœa, Neis. meningitidis, Cl. welchii, Cl. septicum, C. diphtheriæ, B. anthracis, Actino. bovis, Tr. pallidum, Tr. pertenue, Bor. vincenti, Bor. novyi, Lep. icterohæmorrhagica.*

The following bacteria are resistant to the action of penicillin in therapeutic concentration: *E. typhosum, Sal. paratyphi, Shig. dysenteriæ, B. coli, B. proteus, Ps. pyocyanea, Myc. tuberculosis, H. influenza, H. pertussis, Bruc. abortus, Bruc. melitensis, Past. pestis, Past. tularensis, Blastomyces, Monilia albicans, Plasmodia, Trypanosomes, Leishmaniasis,* viruses, excluding psittacosis. A large number of gram +ve organisms are thus sensitive to penicillin and many gram −ve bacteria resistant. Some strains of susceptible bacteria, normally susceptible to the drug, may have a natural resistance and require higher concentrations of the drug to destroy them. Where a pathological service is available the organisms causing an infection should be isolated and their sensitivity to penicillin determined, and dosage can be controlled by estimations of penicillin serum levels. Very ill patients should not await a bacteriological investigation. In general practice a clinical diagnosis is often sufficient, provided that adequate dosage is used and treatment is not continued beyond 48 hours if there is no response. In many acute infections the response to treatment is rapid if begun early. Penicillin does not obviate the necessity of such surgical measures as the drainage of abscesses and the removal of necrotic foci. The drug has no action on bacterial toxins and suitable antitoxins should be used where possible, and other measures such as blood transfusions employed where required. Brief reference will be made to the many important diseases in which penicillin has proved valuable. Where possible, the upper limit of doses mentioned in the section on dosage should be administered.

SEPTICÆMIA AND BACTERIÆMIA.—These may occur as complications of many of the diseases mentioned below. Large doses should be given intravenously or intramuscularly, either by continuous drip or at 3-hourly intervals. When the bacteriæmia has disappeared 200,000 units 12-hourly should be continued for 4 or 5 days. Surgical treatment of any infective focus may be required.

CARDIOVASCULAR DISEASES.—(1) Subacute bacterial endocarditis 0·5 mega-unit daily, intramuscularly, at 3-hourly intervals or by continuous drip. Continue treatment for 4 weeks or, in the event of relapse, give a second course for 6 to 8 weeks. (2) Suppurative pericarditis. Systemic therapy is combined with installation of 20,000 units daily into the pericardial sac after aspiration of the pus. (3) Infective phlebitis, including lateral and cavernous sinus thrombosis, 0·5 to 1 mega-unit daily, plus surgical treatment if the lateral sinus is involved.

RESPIRATORY DISEASES.—(1) Pneumonia: Penicillin should be used in large doses i.m. for staphylococcal pneumonia. It is also indicated in other pneumonias which are (*a*) sulphonamide-resistant, (*b*) very ill and toxic, (*c*) anæmic and leucopenic, or (*d*) have renal impairment. In bronchopneumonia with mixed infections give penicillin with sulphonamides. Penicillin has no action in primary atypical pneumonia. (2) Empyema: Penicillin is injected into the empyema cavity, 100,000 units daily or 240,000 units every 2 days, following pleural aspiration. If there is an active underlying pneumonia present give intramuscular injections as well. Intercostal drainage or rib resection should be carried out when necessary. (3) Bronchitis: Penicillin inhalations may be of value, supplemented by systemic therapy in severe cases. (4) Bronchiectasis: Frequent courses of penicillin inhalations may be of value. (5) Lung abscess: Systemic therapy, alone, may cure some cases. If surgical drainage is necessary it can be combined with local application of a solution 500 to 1,000 units per mil.

MOUTH AND THROAT.—(1) Vincent's angina: Treat with lozenges, pastilles or wafers for 4 or 5 days. Prolonged therapy may cause soreness of the mouth. (2) Acute parenchymatous glossitis requires systemic therapy. (3) Pyorrhœa: Give large dose i.m. just before dental extractions or insert dental cones containing penicillin into sockets. (4) Acute pharyngitis, tonsillitis and laryngitis: Penicillin should be used as a spray, either directly or by inhalations. Severe cases, or where quinsy threatens, require large doses intramuscularly. Lozenges may be given after tonsillectomy. (5) Scarlet fever: Systemic penicillin is combined with antitoxin and is of value in preventing septic complications. (6) Diphtheria: Large intramuscular doses are a valuable adjunct to antitoxin in severe cases and are also of value for carriers.

NOSE.—(1) Rhinitis: Penicillin spray, 1,000 to 10,000 units per ml., which can be combined with ephedrine 1%, is useful in eliminating secondary invaders following a cold and should be applied 2-hourly. An alternative is a penicillin snuff or cream. (2) Sinusitis: ¼ to ½ mega-unit intramuscularly, 12-hourly for 2 or 3 doses, combined with penicillin inhalations. If pus develops it must be evacuated, followed by lavage of the cavity with penicillin solution.

EAR.—(1) External otitis: Local application of cream, or aqueous or oily drops containing penicillin. (2) Otitis media: In acute cases give large intramuscular doses; after perforation of drums combine with insufflation of powder or installation of solution, 2,000 units per ml., into the canal. Chronic cases with mixed infections may require oral and local sulphonamide therapy as an adjunct. (3) Mastoiditis: Systemic therapy with large doses combined with local applications after cortical mastoidectomy.

EYES.—Although penicillin does not readily penetrate into the eye, the use of pure penicillin, which is much less irritant, has made possible the administration of high concentrations (an ointment of 30,000 units per gram or a solution of 30,000 units per mil. injected subconjunctivally) which will penetrate into the aqueous and even vitreous humour. Eye drops, 2,500 units per mil., are generally used and should be applied hourly, or in ophthalmia neonatorum every few minutes for ½ hour. An ointment can be used as an alternative. Blepharitis, styes, purulent conjunctivitis, ophthalmia neonatorum, keratitis, corneal ulcer and hypopyon ulcer are indications for penicillin. Severe or deep ocular infections such as irido-cyclitis require systemic penicillin as well.

NEUROLOGICAL DISEASES.—(1) Meningitis: Intrathecal administration (see above), 10,000 to 20,000 units daily, or even 12-hourly, in early stages. Pure penicillin makes possible the use of even larger doses, *e.g.* 50,000 units, without meningeal irritation. Rigid asepsis is necessary to avoid contamination by penicillin-resistant bacteria. Lumbar injection is the safest route but spinal block may necessitate cisternal or intraventricular injections. Systemic penicillin should be given as well, and large doses should be used in pneumococcal meningitis, and the simultaneous administration of sulphonamides, particularly for the latter, is advisable. Any primary focus of infection, *e.g.* otitis media or mastoiditis, must be treated. (2) Brain surgery (cerebral abscess or trauma): Pure penicillin should be used if possible as it is less irritant. In cases of trauma, penicillin-sulphathiazole powder can be applied prophylactically. In cases of infection, the installation of solution, 1,000 units or more per ml. twice daily, after evacuation of pus should be carried out.

SKELETAL INFECTIONS.—(1) Acute osteomyelitis. Large systemic doses are combined with routine treatment such as eradication of primary foci, immobilisation, evacuation of abscesses and installation of local penicillin. (2) Chronic osteomyelitis. Give systemic penicillin for 2–6 weeks plus local penicillin into sinuses combined with other necessary surgical measures. (3) Pyogenic arthritis. Systemic penicillin is given for the associated general infection but does not readily penetrate the synovial membrane. The infected joint should be aspirated and the fluid replaced by penicillin solution, 50,000 to 100,000 units. Prophylactic penicillin is valuable in cases of surgery to bones and joints to prevent infection.

OBSTETRICS AND GYNÆCOLOGY.—(1) Puerperal sepsis. Prophylactic intramuscular penicillin is given to prevent infection after difficult and instrumental deliveries. When sepsis occurs give large doses, particularly in septicæmia. In thrombophlebitis, systemic penicillin is combined with heparin or dicoumarine. (2) Cracked nipples. Use penicillin cream. (3) Breast abscess. Systemic penicillin, plus aspiration of pus and replacement by penicillin solution. Surgical drainage may be required. (4) Salpingitis and pelvic cellulitis. Give large systemic doses.

URINARY INFECTIONS.—(1) Pyelitis, pyelonephritis, perinephric abscess, cystitis. These infections, if due to penicillin-sensitive organisms, may respond to systemic therapy, but this may have to be prolonged in chronic cases. (2) Nephritis. Systemic therapy is of value in treating the causal streptococcal focus and it may thus benefit acute nephritis occasionally. Large doses, 400,000 to 800,000 units daily, may even prove effective in infections due to some strains of the relatively insensitive gram negative bacilli.

GASTRO-INTESTINAL DISEASES.—(1) Acute appendicitis, acute cholecystis, acute peritonitis. Whilst *B. coli* is resistant to penicillin, susceptible bacteria such as streptococci may be present in these conditions, and improvement may follow large doses combined with surgery when indicated. (2) Peritonitis. Large doses indicated in pneumococcal, streptococcal or gonococcal cases. (3) Typhoid fever. 200,000 units intramuscularly 2-hourly, plus sulphathiazole 1 gram 4-hourly, for 4 days, followed by a second course after 2 days' interval, has been found of value because of a synergistic action between the two drugs against E. typhosum. This treatment, however, has not proved very effective against typhoid carriers. (4) Ulcerative colitis and amœbic dysentery. Systemic therapy may benefit secondary infection with penicillin sensitive bacteria.

SKIN DISEASES.—Penicillin of value in infective dermatoses due to penicillin-sensitive organisms. (1) Impetigo, *sycosis barbæ*, secondarily infected eczema, pyoderma and tropical ulcer: treat with penicillin cream, ointment, powder or lotion, the latter as a spray or compresses. In sycosis prolonged therapy required. (2) Carbuncles and boils: 0·5 mega-units twice daily for 2 or more days may abort early cases. Local treatment with cream, powder or lotion for discharging lesions or if excision has been carried out. The alternative is to inject penicillin, 2,500 units per ml. around the lesion. (3) *Dermatitis herpetiformis*: use systemic therapy. (4) Cellulitis, erysipelas, lymphangitis, lymphadenitis: large doses intramuscularly combined with local therapy if there are discharging sinuses or after incision. (5) Burns: treat with penicillin cream. (6) Paronychia: penicillin should be used where necessary after evacuation of pus under the nail. (7) Whitlows and infected tendon sheaths: large intramuscular doses, plus local application of cream or solution if incision becomes necessary.

WOUNDS.—Initial therapy with cream or penicillin-sulphathiazole powder. Infected wounds should be treated with lotion, cream or powder, plus any necessary surgery. Systemic therapy is employed where there is generalised infection or, prophylactically, for large lacerated wounds or compound fractures. Gas gangrene may be prevented by above prophylactic treatment. If it occurs give massive doses of penicillin intramuscularly, plus gas-gangrene antitoxin, also irrigate with penicillin lotion through tubes placed in the wound.

VENEREAL DISEASES.—(1) Gonorrhœa: give 150,000 units intramuscularly 2-hourly for 5 doses or 200,000 units repeated in 4 hours. In females, 200,000 units 2-hourly for 5 doses and if there is pelvic suppuration continue with 200,000 units daily for 5 days. For chronic or relapse cases prolonged treatment up to 1·5 mega-units, plus sulphonamide, or fever therapy may be required. Abscesses, *e.g.* prostatic, require evacuation. One injection, 300,000 units of the oily suspension, has been used, but it is difficult to administer. Successes have been recorded for oral therapy to ambulant cases, giving 40,000 units plus 1 gram sodium citrate 3-hourly for 6 doses. For treatment of ophthalmia and irido-cyclitis, see above. (2) Syphilis: penicillin should only be used in association with arsenical or bismuth therapy. Its ultimate value remains to be assessed, particularly for later cases. The following courses have been recommended: 40,000 units intramuscularly 3-hourly for 7½ days to a total of 2½ million units combined with 10 daily injections of ·09 grams Neohalarsine (see oxyphenarsine, p. 144) or 0·06 grams Mapharside. If toxic symptoms develop, discontinue arsenic and increase total penicillin dosage to 4 million units over the same period. Combined treatment with bismuth injection is successful in preventing relapses. In neurosyphilis give 4,800,000 units in 7½ days plus arsenic and bismuth, such systemic therapy is of value despite the fact that only small amounts of penicillin pass the "blood brain" barrier. Ambulant treatment with large single daily doses has been encouraging, *e.g.* 300,000 units daily for 13 days or 500,000 units daily for 8 days for primary syphilis, and similar doses for 16 and 10 days respectively for secondary syphilis. Congenital syphilis can be prevented by adequate treatment of the mother in pregnancy, giving her a total of 2,400,000 units, beginning with small doses of 50,000 units daily for 2 or 3 days and prolonging the course for 8 or 9 days to prevent a Herxheimer reaction. Treat congenital syphilis by giving the baby 20,000 to 40,000 units 3-hourly for 10 to 15 days in order to avoid therapeutic shock and precede this treatment by 2 weeks of arsenic therapy.

MISCELLANEOUS DISEASES.—(1) Other spirochætal infections such as rat-bite fever, Weil's disease, relapsing fever and yaws are indications for penicillin. (2) Actinomycosis: penicillin of value in early cases provided that the particular strain is sensitive to the drug. Give 200,000 units twice daily for 3 weeks and repeat for 2 or 3 courses at intervals of 2 weeks. Insert penicillin solution into sinuses and abscesses. Combine with surgery in chronic cases. (3) Anthrax: initial dose 0·5 mega units followed by 100,000 units 3-hourly for 3 or 4 days. (4) Agranulocytosis: penicillin is useful in treating the secondary infections complicating this disease and is used in conjunction with pyridoxin, pentose nucleotide, etc. (5) Rheumatic infection: pastilles of 500 units given thrice daily over a period of many months are claimed to reduce the incidence of sore throats and subsequent rheumatic manifestations. (6) Parenteral infections in infants.

The following is the current list of official penicillin and its preparations:

Penicillium, Calcium and Sodium Salts of.
Injectio Penicillini.
Injectio Penicillini Oleosa.
Cremor Penicillini.

Cremor Penicillini Sterilisata.
Oculentum Penicillini.
Trochiscus Penicillini.
Unguentum Penicillini.

Streptomycin.

This is an antibiotic substance derived from a species of streptothrix (Actinomyces griseus). It was isolated in America and at present only small quantities are available in this country for clinical trials. Its ultimate value in therapeutics is still, to some extent, *sub judice*. It is prepared as the hydrochloride or sulphate and is a yellow powder, 1 gramme of the pure substance being equivalent to 1 million units. Originally it was standardised in terms of its antibacterial activity against *E. coli*. It is soluble in water and although very thermostable is best stored in a refrigerator. Its antibacterial activity is most marked in a slightly alkaline medium. It is insoluble in liquids, such as those of tuberculous caseous tissues. It has an antibacterial action against many organisms: *E. coli; E. typhosum; S. paratyphi; S. enteritidis; S. dysenteriæ; Prot. vulgaris; B. pyocyaneus; pneumococcus; H. influenza; H. pertussis; Staph. aureus* (some strains); *Myc. tuberculosis; Bruc. melitensis; Bruc. abortus; Past. tularensis; Past. pestis.* Variation occurs in its action against different strains. It is much more effective against many gram negative organisms and the tubercle bacillus than is penicillin. The gram positive cocci are more resistant to the drug in the presence of body fluids. It is not destroyed when given by mouth, but little is absorbed and much of the drug is recovered from the fæces. Not much is absorbed after inhalation. It must be injected, usually intramuscularly to produce a systemic effect. Although it can be administered by continuous intravenous drip, dissolving the daily dose in 1 to 2 litres of normal saline, the drug or its impurities may give rise to reactions. Oral administration is only intended for an antibacterial action against the bowel organisms. The drug can also be applied locally or injected intrathecally or into one of the body cavities. After injection it is rapidly absorbed and excreted by the kidneys.[1] It diffuses rapidly throughout the body and appears in the bile and during pregnancy in the fœtal circulation. *In vitro* tests of the sensitivity of the causal organisms to streptomycin should be carried out but are not an infallible guide to the clinical response to the drug. Bacteria may develop resistance to the drug and this sometimes occurs rapidly. A di-hydro-streptomycin is at present on trial.

Favourable therapeutic results are recorded in: (1) Bacteriæmia and septicæmia due to gram negative bacteria sensitive to the drug. (2) Meningitis due to *H. influenza*. Despite the diffusion of small amounts of the drug into the C.S.F., more so in meningitis, it is best to administer the drug intrathecally and to give antiserum and sulphonamides as well. (3) *Tularæmia*. (4) Urinary infections due to *Prot. vulgaris, Aerobact. ærogenes, E. coli, B. pyocyaneus*. The drug acts best in an alkaline urine, but is not very effective if there is urinary obstruction. (5) Pulmonary infections due to *B. friedlander* and *H. influenza*. The drug is also used for the eradication of sensitive bacteria from the respiratory tract prior to operation. (6) Peritonitis due to gram negative organisms. (7) Tuberculosis. The ultimate value of the drug in this disease is still uncertain despite favourable clinical and experimental evidence. It appears to be of definite value in external tuberculous sinuses, *lupus vulgaris*, tuberculous laryngeal and tracheobronchial ulceration, acute miliary tuberculosis and tuberculous meningitis, tuberculous peritonitis, tuberculous ulceration of the tongue and tuberculous enteritis. In pulmonary tuberculosis it appears to benefit non-confluent lesions with a recent spread. Cases of genito-urinary tuberculosis may show some improvement. Results in bone and joint tuberculosis are at present inconclusive. The drug is also being tested in combination with members of the Promin group (*q.v.*). (8) Enteritis and colitis, but not enteric fever, cholera or ulcerative colitis may benefit by oral administration of 2 to 3 gm. daily. (9) Infected wounds, where it should be used as an adjunct to surgery. (10) Gonococcal arthritis, resistant to penicillin and sulphonamides. The drug may also prove of value in plague and lymphogranuloma inguinale. It is less effective than penicillin in syphilis.

Dosage: Streptomycin should be dissolved in normal saline before use. For intramuscular administration, solutions contain 100 to 200 mg. per ml. The drug is given 4-hourly, the daily dose being 2 to 4 gm. In tuberculosis the daily dose recommended varies from 1 to 3 gm. For intrathecal injection, 100 mg. in 10 ml. normal saline are given every 24 to 48 hours after withdrawing C.S.F. Oral administration is given at 6-hourly intervals, the daily dose being 2 to 3 gm. Nebulisation is carried out for its local action on the respiratory tract and can thus be used to supplement intramuscular therapy. The solution employed contains 50 mg. per ml. Local injection into empyema and abscess cavities is performed with solutions containing 10 to 100 mg. per ml. but it is not of much value in tuberculous empyema.

The drug, if injected in doses of 0·4 gm. 4-hourly, gives an average blood concentration of about 15 micrograms per 100 ml., and the "24 hours urine" shows 1,000 to 4,000 micrograms per 100 ml. The course of therapy ranges from 5 to 14 days, except in tuberculous patients, where it is carried on for weeks or months.

Toxic Symptoms: Some of these are due to impurities. The following reactions may occur: (1) Pain at the site of injection. (2) A histamine type of reaction with flushing, headache and fall in blood-pressure, and due to impurities. (3) Allergic reactions, with maculopapular or urticarial rashes, pyrexia, joint swellings, nausea and vomiting, and eosinophilia. Antihistaminic drugs (*q.v.*) appear to benefit these symptoms. (4) Renal irritation with casts may occur if the urine is acid, and appears to be due to the drug itself. (5) Disturbed vestibular function, with vertigo, tinnitus and occasional deafness, occurs most commonly during the 3rd and 4th weeks of treatment, and is probably due to the drug itself, particularly with excessive dosage. Individuals handling the drug may develop dermatitis and should wear rubber gloves.

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[1] The drug can be recovered from the urine for further therapeutic use.

Tyrothricin.

This is a bactericidal substance produced by *Bacillus brevis*. It contains gramicidin, the active bactericidal principle, and tyrocidine which increases the solubility and stability of gramicidin. It is effective against many gram positive organisms (staphylocicci, streptococci, pneumococci, diphtheria bacilli, etc.) but is ineffective against gram negative organisms. The bactericidal action is not reduced by blood or pus. **It must only be administered topically,** and is used (1) by irrigation or wet packs in infections of the skin and soft tissues, ulcers and osteomyelitis; (2) by irrigation for empyema, sinusitis, otitis media and mastoiditis; (3) as a spray for throat infections; (4) as drops for eye infections. If there is increase in pain following its use the concentration of the drug must be reduced. Parenteral administration in animals causes toxic changes in the liver and heart. It is supplied as a 2% solution in alcohol, diluted before use with sterile water to form a fine suspension, a concentration of 33 mg. per 100 ml. being generally employed. Resistant bacteria may respond to higher concentrations which should not exceed 50 mg. per ml.

Gramicidin S.

This compound, produced by a *B. brevis* variant, is widely used in Russia and has been isolated in crystalline form. It is a peptide and is claimed to be much more effective than tyrothricin. It has the advantage of being effective against some gram negative bacteria such as in dysentery and some strains of *B. paratyphosum A* and, experimentally, will also control anærobic infections. It is said to assist epithelialisation of wounds. Clinical indications are the same as for tyrothricin and it is used also in the preparation of cow pox vaccine to kill contaminating organisms. It is employed in aqueous solution 400 μg per ml.

Other antibiotic substances have been isolated but have so far not received any large clinical trials. Conclusions as to their ultimate value cannot, therefore, be drawn at present. **Bacitracin,** prepared from an aerobic gram positive sporing bacillus, is effective against gram positive cocci. **Mycocidin,** prepared from a mould, is active against the tubercle bacillus. **Mycophenolic acid,** prepared from *penicillium brevi compactum,* inhibits gram positive organisms. **Aerosporin,** a stable substance, is an antibiotic produced by *B. ærosporus.* It is a base and is effective experimentally against *S. typhi, B. coli* and *H. pertussis.* **Polymyxin** is a similar antibiotic, receiving trials against pyocyaneus, pertussis and abortus infections. **Chloromycetin** is derived from streptomyces, is active against *Staphylococcus areus, bacterium coli,* Friedlander's bacillus, *Proteus vulgaris, S. paratyphi, S. paradysenteriæ, H. pertussis,* tubercle bacillus and rickettsial infections. **It is effective orally in doses of 6 gm. daily in typhus.** It has very low toxicity.

The Antimalarials

The mode of action of the antimalarial drugs will be first considered. The sporozoites injected by the mosquito into the human host are themselves not susceptible to the action of any of these drugs. They develop, however, into exo-erythrocytic forms which can be demonstrated in avian malaria, and probably exist as a transient phase in human malaria before developing into the intracorpuscular forms of the parasite. (1) Proguanil (*q.v.*) and pamaquin, but not quinine and mepacrine, attack these exo-erythrocytic forms, which are thus prevented from developing into the erythrocytic stages. Proguanil and pamaquin are therefore causal prophylactics. In subtertian malaria the exo-erythrocytic forms are destroyed and the drugs are true causal prophylactics. In benign tertian infections these forms are only inhibited, and the development of the intracorpuscular stages delayed, so that the drugs are partial causal prophylactics, delayed attacks of malaria occasionally occurring when prophylactic therapy is discontinued. As will be apparent later, proguanil is much superior to pamaquin as a causal prophylactic because it is practically non-toxic. (2) The asexual erythrocytic forms, including the schizonts, are killed by proguanil, quinine, mepacrine, resochin and sulphadiazine (but not pamaquin), and these drugs are therefore schizonticidal. When used **prophylactically** this group of drugs, with the exception of proguanil, do not prevent the appearance of erythrocytic forms, but destroy them after they have developed. Thus they suppress clinical symptoms and are termed schizonticidal suppressants. As is the case with the causal prophylactics, the schizonticidal suppressants are more effective in subtertian than benign tertian infections for, in the latter disease, delayed attacks may occur when prophylactic treatment is stopped, presumably because of persisting exo-erythrocytic forms. The schizonticidal drugs, if present in adequate concentration, are effective in the treatment of overt malaria as the erythrocytic forms are rapidly destroyed. In subtertian malaria cure is generally complete, but in benign tertian disease relapses may occur when the drug is discontinued because of persistent exo-erythrocytic forms. The sexual phase of the parasites or the gametocytes are killed by pamaquin, but not by the schizonticidal group. Pamaquin is therefore effective in rendering patients and carriers non-infective to mosquitoes. Proguanil, although it does not kill the gametocytes nor change them morphologically, does affect them in some way which prevents maturation of the parasite in the mosquito, if the latter is infected with a patient or carrier taking the drug.

Mepacrinæ Hydrochloridum, Off. ¾–1½ gr. (*Atebrin**).

Mepacrine hydrochloride is a complex derivative of acridine, which occurs as a yellow crystalline powder having a bitter taste. Taken by mouth it is rapidly absorbed, but only slowly excreted, in the urine which becomes yellow; there is, therefore, some cumulation of the drug in the body. Its antimalarial efficacy depends upon its concentration in the blood; it concentrates more in the corpuscles, particularly the white cells, than in the plasma. The bulk of the drug is stored in the tissues. Its mode of action has already been discussed. The drug is used as a suppressive in prophylaxis and as a curative agent against overt malaria. It is more effective in subtertian than in benign attacks. Rapid relief of symptoms is obtained by giving the drug orally, 0·2 gm. 6-hourly for two days, followed by 0·1 gm. thrice daily for five days. Each dose may be taken with sodium bicarbonate 1 gm. in ½ pint water. The estimation of the drug in the blood or urine is sometimes done to determine whether absorption has been adequate. However, if there is vomiting, diarrhœa, or if the condition is severe, it is better to administer the drug parenterally (see below). If cumulation occurs the skin displays a well-defined yellow tinge. It is a useful drug to replace quinine in cases of idiosyncrasy to the latter during pregnancy and for patients with blackwater fever. It may also be combined with quinine. It will, however, probably be replaced by paludrine. The suppressive (prophylactic) dose is 0·1 gm. daily. The drug has been successfully used as an alternative to quinidine in auricular fibrillation. Headaches, malaise, vomiting, colic and mental disturbances are indications of overdosage or idiosyncrasy.

Mepacrinæ Methanosulphonas (*Aterbrin musonate**), Off. ¾–1½ gr.

Solution of mepacrine methanosulphonate, 3% in sterile water, is used by intramuscular injection in severe cases of malaria. The solution must be freshly made at the time of injection and no heat used in its preparation.

Proguanil (*Paludrine**).

This compound, synthesised in 1945, is N-p-chlorophenyl-N-isopropyl biguanide. It is a colourless and slightly bitter substance. It is very active against avian malaria, and clinically has proved effective in subtertian and benign tertian malaria, including primary, delayed primary and relapse cases. It is thought to act by interfering with some enzyme or co-enzyme system concerned with nuclear metabolism. As compared with the other antimalarial compounds it has the widest range of action against the parasites, for not only is it a causal prophylactic and schizonticidal drug but, in addition, it interferes with the development of the gametocytes in the mosquito. It is more effective in subtertian than in benign tertian malaria for, in the latter, delayed attacks occasionally follow prophylactic and relapses curative therapy when the drug has been discontinued. The relapse rate in benign tertian infections is not reduced by giving large doses of the drug for as long as two weeks, and is about the same as with mepacrine, but greater than that following a combined course of quinine and pamaquin. It appears, however, that if small doses of the drug are given for about six months the occasional relapses or delayed attacks may be satisfactorily prevented (see below). Paludrine has a wide range of therapeutic activity and is virtually non-toxic, which gives it a great advantage over quinine, mepacrine and pamaquin. Nausea and vomiting may occur with large doses of 500 mg. daily.

The dosage recommended for subtertian malaria is 100 to 200 mg. orally twice daily for 14 days. In benign tertian infections an initial dose of 300 mg. will cure the clinical attack, and this should be followed up with 100 mg. weekly for six months to prevent relapses. As a causal prophylactic the drug can be given in doses of 100 mg. once or twice weekly.

Pamaquin, Off. $\frac{1}{3}$–$\frac{3}{5}$ gr. (*Plasmoquine**).

Pamaquin, a bitter-tasting yellow powder, is a complex quinoline derivative. It is administered by mouth in the treatment of malaria. Because it has no schizonticidal action but destroys the gametocytes, it is common practice to administer the drug in conjunction with quinine. A useful course for the treatment of relapses in benign tertian malaria is pamaquin $\frac{2}{5}$ gr., plus quinine hydrochloride 10 gr. daily, for one week, repeating the course after an interval of four days. The two compounds are sometimes combined in one tablet (Quino-Pamaquin). An alternative course is to use a similar dose of pamaquin with paludrine 300 mg. daily for 10 days. Pamaquin, because of its gametocidal action, will render patients and carriers non-infective to mosquitoes. The spread of infection is thus reduced. Pamaquin is slowly excreted by the kidneys, and it is usual to give it three times daily for one week, followed by a four-day intermission to prevent cumulation. This course is repeated four times. Renal, hepatic or cardiac disease are strong contraindications, since there is little margin between the therapeutic and toxic dosage. It is unusual to use larger doses than 0·02 gm. ($\frac{3}{10}$ gr.). Toxic symptoms include severe methæmoglobinæmia and cyanosis, which may develop rapidly. **Mepacrine should not be used concurrently with pamaquin as severe abdominal pain and other toxic effects may develop.**

Quinine Sulphate, 1–10 gr.

Quinine is an alkaloid of cinchona bark. Its mode of action as an antimalarial drug has been already described and depends upon its schizonticidal activity. Like mepacrine it is more effective in subtertian than in benign tertian infections for, in the latter disease, delayed attacks may follow suppressive therapy and relapses curative treatment when the drug has been stopped. As a suppressive (prophylactic) it is used in doses of 5 gr. daily, and in treatment in doses of 10 to 30 gr. daily. Best results are obtained by giving the drug 2 or 3 hours before the onset of fever, so that a maximal concentration of the drug in the blood may develop when schizogony occurs. Such calculation obviously can only be made in the case of periodic fever. Courses of quinine therapy are usually given for a week, although shorter courses of two or three days may be followed by mepacrine for a week, and then after an interval of a few days by a final course of pamaquin. In severe malaria the intravenous infusion of quinine dihydrochloride 0·6 gm. in 100 mls. of normal saline may be necessary. Quinine sulphate is not very soluble in water, and when prescribed in mixture form a small dose of a mineral acid should be added. For pills and tablets either quinine disulphate or the hydrochloride are preferable. Quinism (Cinchonism) results from overdosage or idiosyncrasy and may produce headache, tinnitus, deafness, vertigo and visual disturbance. Quinine sulphate is used empirically in the treatment of disseminated sclerosis, the dosage recommended is 5 grams twice a day, or less if quinism develops.

Other therapeutic applications of quinine are only justified when world shortage does not exist. Taken by mouth its soluble salts act as bitters (*q.v.*). After absorption the drug is thought to exert a tonic action on smooth muscle, and it is occasionally used with castor oil to induce leads to the putting on of weight and an improved sense of general well-being. Arsenic is believed to activate iron for the formation of hæmoglobin, and small doses are combined with iron in the treatment of hypochromic anæmias. The drug is used, also, against furunculosis and in other, especially chronic, skin conditions. Arsenic being slowly excreted by the bowel and in the urine is a cumulative poison. Acute poisoning with inorganic arsenic is characterised by severe gastro-enteritis with collapse and, later, nephrosis and liver damage. Pigmentation of the skin, rashes, herpes, polyneuritis, coryza, blepharitis, laryngitis, anæmia, mental degeneration, cardiac failure and toxic jaundice are associated with chronic poisoning. The drug can be found in the hair and urine.

Treatment is eliminative with the aid of sodium thiosulphate 10 mls. of a 10% solution intravenously. Dehydration and exhaustion may be combated with intravenous dextrose-saline and stimulants. In acute poisoning the stomach should be repeatedly washed out with a mixture of milk and water under anæsthesia or with a mixture of freshly precipitated ferric hydroxide and magnesium oxide in aqueous suspension.

Liquor Arsenicalis (Fowler's Solution), Off. 2–8 min.

A suitable preparation for adding to mixtures.

Liquor Arseni et Hydrargyri Iodidi (Donovan's Solution), 5–15 min.

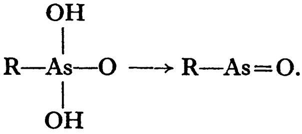
Solution of arsenic and mercuric iodide may be administered by mouth in the treatment of tertiary manifestations of syphilis.

Organic Arsenicals

An organic arsenical is a compound in which the arsenic is in direct combination with a carbon atom. When freshly dissolved the arsenic in such compounds is not ionised, and this appears to account for their reduced toxicity as compared with the inorganic arsenicals used in medicine. Among the organic arsenicals formerly employed in medicine were various salts of cacodylic acid, and later, research by Ehrlich led to the introduction of *Atoxyl*,* a pentavalent compound used for a time in the treatment of trypanosomiasis. Later still came the discovery of *Salvarsan** (or 606), a milestone in chemotherapeutic progress. These preparations have been superseded entirely by a great number of more modern organic arsenicals which have the advantages of reduced toxicity and, in some cases, of ease of administration. These compounds are used particularly in the treatment of syphilis in all forms, as well as of certain tropical diseases, including yaws and amœbiasis. They comprise two groups: (*a*) trivalent compounds which include neoarsphenamine, sulpharsphenamine, *Stabilarsan*,* *Mapharside** (*Mapharsen**); and (*b*) the pentavalent compounds acetarsol, carbasone and tryparsamide. The mechanism of action of these compounds is not yet elucidated, but they certainly undergo some form of activation in the tissues. Experimental evidence indicates that the trivalent and, to an even greater extent, the pentavalent compounds have a much slower action in destroying trypanosomes than has arsenious oxide, and it is suggested that this delay is due to conversion of the compounds used into complex derivatives of arsenious oxide, viz.:

For trivalent compounds: $R\!-\!As\!=\!As\!-\!R \longrightarrow R\!-\!As\!=\!O$.

For pentavalent compounds:[1]



$$R\!-\!\underset{\displaystyle OH}{\overset{\displaystyle OH}{As}}\!-\!O \longrightarrow R\!-\!As\!=\!O.$$

The "arsenoxide" is thought to react with glutathione, which is present in the trypanosomes as well as the tissues, and to kill the former by interference with the oxidation-reduction mechanism.

All the organic arsenicals can give rise to capillary endothelial damage, and toxic effects include, also, hæmorrhagic encephalitis, exfoliative dermatitis and other skin rashes, nephrosis and blood dyscrasias. A more complete account of these reactions appears later in this chapter.

To minimise risk of toxic action, premedication with alkalis, dextrose and calcium is often advised, and in treatment of arsenical poisoning the same measures are adopted together with intravenous injection of sodium or calcium thiosulphate, BAL, etc. (see below).

Sodium cacodylate, a pentavalent compound, has a similar but less toxic action than inorganic arsenic, but is seldom used. The oral dose (60 mg.) is smaller than the hypodermic one (200 mg.) because inorganic arsenic is liberated in the stomach by peptic acid.

Acetarsol (*Stovarsol**), 1–4 gr.

This drug possesses the advantage over the arsphenamines (*v. infra*) in being active when administered orally, it is thus particularly useful in congenital syphilis. It is insoluble in water and is usually given as a powder or tablet, and its indications are similar to those of the arsphenamines. Recent references to its use in lambliasis are favourable. Acetarsol has been employed in the treatment of chronic amœbiasis. In powder or special tablet form, usually combined with lactose, it may be inserted in the vagina for the treatment of trichomonal vaginitis. A solution of the soluble sodium salt has been used for injection.

Carbasone (*Leucarsone**).

This compound is used in chronic amœbic dysentery, usually following a course of emetine and diodoquin (*q.v.*). It is given in doses of 7½ gr. daily for ten days, and a second course after a week or two may be required. Like other arsenicals it should not be used in the presence of liver or renal damage. Otherwise, arsenical complications are rare. Resistant cases of amœbiasis may be given retention enemata of 2 gm. of the drug in 200 ml. of 2% sodium bicarbonate solution. The drug is also effective in tropical eosinophilia.

Neoarsphenamina, 2½–14 gr. (*N.A.B.,* Neosalvarsan**).

This complex arsenical is the modern improvement on Ehrlich's original "606," which it more conveniently replaces. It is unstable, and becomes increasingly toxic in aqueous solution, and the dry powder is supplied in air-evacuated, sealed ampoules for dissolving in sterile water (B.P. quality)

[1] It is worth remarking that part of the original theory of Ehrlich was that his pentavalent *Atoxyl** became reduced to a more active trivalent compound.

at the time of administration. Although the drug has no effect on the spirochæte *in vitro*, when administered **intravenously** it causes the organism rapidly to disappear from the primary and early secondary lesions of syphilis. It is used, also, in tertiary syphilis, but is of less benefit in neurosyphilis (see reference later to Jarisch-Herxheimer reaction). Neoarsphenamine is used, also, in the treatment of relapsing fever, yaws, anthrax, tropical eosinophilia, rat-bite fever, and in the early stages of disseminated sclerosis as well as in abacterial pyuria. It is applied locally as a 3% solution in glycerin, against Vincent's angina. Neoarsphenamine should not be used intramuscularly as it is highly irritant, and acute cellulitis may develop. Early anaphylactoid reactions which may follow the intravenous injection can be treated by the intramuscular injection of adrenaline solution.

Scheme of Dosage with Arsphenamines

The following scheme of dosage with arsphenamines is now authoritatively recommended: Several courses of neoarsphenamine (or other suitable arsphenamine compound in comparable dosage) with three to five weeks' intermission between each course. In the first course, which should last nine weeks, ten injections are given, the adult dosage in the case of neoarsphenamine rising from 0·4 to 0·6 G. The **total amount** of neoarsphenamine for the course is about 5 G. Concurrently with this is given a series of intramuscular injections of a suitable bismuth (*q.v.*) compound. Pregnant women are more apt to develop an arsenic encephalopathy, and in them the maximum dose should be restricted to 0·45 gm. Since arsenic does not readily penetrate the fœtal circulation until the later months of pregnancy, bismuth is also given to prevent congenital syphilis. For combined courses of arsenicals with penicillin, see monograph on latter.

In the United States, large doses of neoarsphenamine have been given by continuous drip infusion into a vein over a period of several days, but there is a danger of a toxic encephalopathy. Oxyphenarsine is preferred for intensive therapy. The use of hyperthermia in cerebral syphilis, and more recently, in the United States, in all stages of the disease, may prove a valuable method of supplementing arsenic and bismuth therapy by destroying those spirochætes which escape the drugs.

Oxyphenarsine (Arsenoxide).

This trivalent arsenic compound is m-amino-p-hydroxy-phenyl arsine oxide, and comprises a substituted arsenious oxide resembling in general structure the activated form to which the commoner arsphenamines are probably converted in the tissues. Two preparations are available, oxyphenarsine hydrochloride, which is known as *Mapharside** (*Mapharsen* in the U.S.A.), and oxyphenarsine tartrate, called *Neohalarsine.** They are stable compounds and, weight for weight, are about four times as potent and ten times as toxic as neoarsphenamine. In syphilis they are given in doses of about a tenth of those employed with neoarsphenamine, *i.e.* for men, 0·04 to 0·06 gm., and for women, 0·03 to 0·04 gm. As these drugs are much more rapidly excreted than the arsphenamines, injections are given two or three times weekly for 12 to 16 weeks. Intensive therapy is sometimes practised, 1 gm. being given in about 10 days, but there is a risk of an arsenical encephalopathy. Other respects in which these drugs differ from neoarsphenamine are: (1) When dissolving them in sterile water they can be shaken without loss of stability; (2) When solutions are allowed to stand they become less and not more toxic; (3) Solutions should be injected **rapidly** to avoid local pain. Toxic symptoms are the same as with the arsphenamines, but there are no vasomotor disturbances. Treatment is frequently combined with bismuth, penicillin or hyperthermia.

*Stabilarsan.**

This is a stable preparation of arsphenamine diglucoside; it appears to consist essentially of 10% *arsphenamine* in 50% dextrose solution. The arsenic content is about 20%, but it is not so active as neoarsphenamine. The dosage is 0·5 to 0·9 gm. by intravenous injection.

Sulpharsphenamina, 1½–10 gr. (*Kharsulphan**).

Sulpharsphenamine occurs as a yellow powder which is supplied in air-evacuated, sealed ampoules, and dissolved in sterile water at the time of use. Its indications and schemes of dosage are the same as for neoarsphenamine, but it is intended for **intramuscular** injection; the injection may be somewhat painful. Its arsenic content is about 20%.

Tryparsamidum, 15–30 gr.

Tryparsamide has not the same antispirochætal action in the tissues as the arsphenamines, and it appears to exert no action in primary and secondary syphilis. It can, however, pass the choroid plexus, and so diffuses from the blood into the cerebrospinal fluid, and it has been used with some degree of success in neurosyphilis. The drug was originally introduced against trypanosomiasis (var. *Trypanosoma gambiense*) and it was its value in the treatment of the nerve manifestations of this disease that led to its trial in neurosyphilis. Tryparsamide can be combined with bismuth therapy and with malarial treatment in syphilis of the central nervous system. The drug is supplied in sealed ampoules and dissolved in sterile water at the time of administration. The solution can be given by subcutaneous, intramuscular or intravenous injection, in doses of 2 gm. at weekly intervals for 10 weeks.

In view of the very great practical importance of the subject, the following amplification of the possible toxic sequelæ from organic arsenicals is included:

Toxic Reactions with Organic Arsenicals

1. Cellulitis, if a drug like neoarsphenamine is injected outside the vein.
2. Reactions due to the sterile water containing pyrogens (protein shock) or traces of copper ion which promotes ionisation and so increases toxicity.

Toxic reactions resulting from the drugs themselves are due mainly to damage to the capillary endothelium and, at autopsy, hæmorrhages have been found in the brain, kidneys, lungs and alimentary tract, as well as degenerative changes in the liver like those of acute yellow atrophy. The symptoms produced by these reactions are according to Harrison:

1. **During or immediately after injection:** Vasomotor or anaphylactoid symptoms such as flushing, urticaria, pains in the gums and teeth.
2. **Within a few hours:** Rigors, vomiting, diarrhœa, cramp, herpes.
3. **From a day to a month or longer:** Albuminuria, stomatitis, headache, amnesia, loss of weight, erythema and dermatitis (very occasionally this takes the form of an exfoliative dermatitis and may be accompanied by nephritis and pneumonia), jaundice, severe cerebral symptoms such as mental confusion, convulsions and coma, blood disorders (thrombocytopenia, granulocytopenia and aplastic anæmia), polyneuritis, temporary increase of syphilitic signs and symptoms. The last mentioned, known as the Jarisch-Herxheimer reaction, may produce dangerous symptoms of complete thrombosis of arteries if the syphilis involves the coronary or cerebral vessels. The risk of jaundice in arsenotherapy is accentuated by any abnormal liability to infective hepatitis.

Precautions in Organic Arsenic Therapy

To minimise risk arsphenamine compounds should not be used for hæmophilics or in subjects with severe visceral disease, liver disease or Addison's disease. Small doses (0·15 G.) should be used to initiate treatment in the case of alcoholics, patients prone to skin disease, diabetics and cases of syphilis of the heart and aorta and brain. Signs of intolerance should be looked for, great care used in the technique of injection, and the patient made to fast for two hours before the injection is made. Albuminuria, jaundice or erythema are contraindications to a further continuation of the therapy, and dosage should be reduced if minor signs of intolerance appear. In the prevention and treatment of jaundice it is suggested that a high protein and carbohydrate diet is most suitable. Adequate sterilisation of syringes is necessary to prevent contamination by the virus of infective hepatitis.

In the **treatment of toxic manifestations** the patient is put to bed if the symptoms are at all severe. Calcium or sodium thiosulphate 0·6–0·9 G. should be given intravenously every other day and 25 mls. of 40% dextrose solution injected intravenously on the intervening days. Liver injection should also be given. Choline or methionine (*q.v.*) may be administered in jaundiced cases. Injection of adrenaline used for early anaphylactoid effects should be used, also, in cases showing cerebral symptoms; in addition, lumbar puncture and venesection should be made for the last-mentioned types. Ascorbic acid is said to benefit the dermatitis. Treatment with BAL (British anti-lewisite) may prove of value.

Dimercaprol (*BAL*) (2·3-dimercapto-propanol), by virtue of its thiol (SH) grouping, forms stable ring compounds with arsenoxides, gold, mercury and other metals and, by thus preventing these metals from reacting with thiol groups in the tissues, diminishes their toxicity and increases their excretion by the kidneys. The drug is valuable in dermatitis, encephalopathy and agranulocytosis produced by these metals. It is of little value in arsenical hepatitis, moreover liver damage may increase the toxicity of BAL itself. A 5% solution in arachis oil is injected deeply intramuscularly in the following dosage: 2 mls. 4 times daily on the first day, twice daily on the 2nd, 3rd and 4th day, and once daily on the 5th and 6th day. It has also been used by inunction in arsenical dermatitis. Toxic symptoms include skin sensitivity, salivation, lachrymation, vomiting, abscess at the site of injection (due probably to secondary infection) and latent tetany. The drug is contraindicated in lead poisoning. It may prove useful in methæmoglobinæmia as it reduces methæmoglobin to hæmoglobin.

Diamidine Compounds

This group of chemotherapeutic substances have been recently introduced for the treatment of certain tropical protozoal diseases such as trypanosomiasis and leishmaniasis. The compounds employed for the purpose are *pentamidine isethionate* and *stilbamidine isethionate.* The former is given intramuscularly as a 10% solution in daily doses of 5 mg. per kilo bodyweight for 10 or more days. Some authorities recommend intravenous injections of 0·5 mg. per kilo, increasing gradually to 2 mg. per kilo. If given intravenously the drug should be injected slowly to avoid a fall in blood-pressure with faintness. The latter can be counteracted by adrenaline or atropine. The drug has also been found effective in relieving pain of myelomatosis. It is given intravenously every other day up to a total of 2·25 gm., the first two doses being 50 and 100 mgms., followed by subsequent doses of 150 mgms. It is interesting to note that in both myelomatosis and kala-azar there is an increase in serum globulin. It would appear that stilbamidine is deposited in myeloma cells, reacting with the ribonucleo-proteins of the cytoplasm. Neuropathy with trigeminal paræsthæsia may occur. Pentamidine may also prove effective in these diseases. Stilbamidine, while inferior to pentamidine in trypanosomiasis, is effective in leishmaniasis. It is used in similar doses to the other compound. Solutions must be freshly prepared or toxic changes in the liver and kidneys may occur. *Propamidine isethionate* has similar properties to the above, but is used mainly as a local antiseptic to infected wounds, burns, etc. It is both bacteriostatic and bactericidal, particularly against streptococci and staphylococci. It is not inhibited by blood or pus. It is employed in a 0·15% concentration as a cream or in a water-soluble gel base. A 0·15% solution is used for chronic conjunctivitis, particularly that due to Morax-Axenfeld bacillus.

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Suraminum, Off. 15–30 gr.

Originally introduced under the name of *Germanin** or *Bayer* 205, this substance is very similar to *Moranyl** and *Antrypol*,* which are derivatives of "trypan red." These drugs are complex urea-sulphonate compounds. Experimentally, they have been shown to be powerful trypanocides, producing both a cure and immunity in infected mice; they have no action *in vitro.* Suramin therapy has proved of value against trypanosoma rhodesiense, but is much inferior to tryparsamide (*q.v.*) against t. gambiense. Best results are obtained in the early stages of infection prior to the development of marked nervous symptoms. Skin rashes and amblyopia may arise from its use, and an acute and fatal nephritis has been reported. The use of a single dose of 2 gm. for prophylaxis has been successful. In treatment, the dosage is 0·5–1 gm. weekly in aqueous solution by intravenous or intramuscular injection, up to a total of 5 gm. Combined therapy with tryparsamide is sometimes adopted, *i.e.* 1 gm. of suramin three times in one week, followed by 2 gm. tryparsamide for 5 doses. Suramin is used occasionally in the treatment of severe pemphigus.

Related urea-sulphonate compounds such as *S.U.P.* 36* have been recommended for the treatment of influenza, colds and a variety of other infections.

Chemotherapy in Cancer and the Reticuloses

Therapeutic advances in this important field have been made during recent years. The value of stilbœstrol in prostatic carcinoma, *q.v.*, depends upon the antagonistic action of œstrogens and androgens. The use of radioactive iodine in thyroid cancer depends upon its interfering with the nutrition of the tumour cells. The mode of action of stilbamidine, *q.v.*, in myelomatosis is to modify cellular nucleic acid metabolism. Certain compounds act as mitotic poisons interfering with mitotic division of the cells. The use of urethane in leukæmia and myelomatosis (*q.v.*) and of the nitrogen mustards in the reticuloses (see below) depends on this factor. Radioactive phosphorus, *q.v.*, in the treatment of polycythæmia is likely to replace older methods of therapy, such as X-rays and phenylhydrazine.

Nitrogen Mustards

Recent developments in chemotherapy have resulted from the observation that "nitrogen mustards" allied to mustard gas affect mitosis and are toxic to the blood-forming tissues, particularly to the actively-dividing cells of the bone marrow and lymph nodes. Two of these compounds have been used in the treatment of neoplastic conditions, and have been found capable of producing remissions, particularly in the relapse phase of lymphadenoma and in polycythæmia. Improvement has also been noted in lymphosarcoma and chronic myeloid leukæmia. The remissions are temporary and the treatment needs to be repeated at intervals of a few weeks. The compounds used are tris (β-chloro-ethyl) amine hydrochloride and methyl bis (β-chloro-ethyl) amine hydrochloride. One scheme of dosage is to give 0·02 mgm. of the drug, per kilo bodyweight, dissolved in 20 mls. of saline. The injection is made very slowly intravenously and is repeated in 24 hours. Toxic reactions include thrombosis of the injected vein, vomiting, marked leucopenia, particularly of the neutrophils, and a fall in hæmoglobin and blood platelets.

ANTISEPTICS AND DISINFECTANTS

An antiseptic, or bacteriostatic, substance is one which will inhibit bacterial proliferation and activity; a disinfectant, or bactericide, is one which kills bacteria. The same substance will often exert either action according to its degree of concentration and the conditions under which its action occurs. In general, the main conditions which influence the efficiency of antiseptics, apart from concentration, are the medium, the duration of contact, the nature of the organism (bacterial spores are particularly resistant) and the temperature which, in rising, lowers bacterial resistance. These factors are utilised in the sterilisation of thermolabile substances, such as Solution of Adrenaline, by heating at a moderately high temperature in the presence of an antiseptic. The medium factor is especially important in respect of antiseptics used on organic tissues. Here the pH of the field and possible chemical reactivity of protein with the antiseptic substance employed are essential considerations. It is essential when testing the qualities of an antiseptic to be used on human tissues to ascertain (1) the extent, if any, to which it injures living tissues, including leucocytes, for this would interfere with healing and natural resistance; (2) the variety of pathogenic bacteria against which it is active; and (3) the extent to which its activity is inhibited by blood or pus. The introductory portion of the chapter on Chemotherapeutic Substances should be read in conjunction with the present chapter.

Alcohol (*q.v.*).

Aromatic Oils and Phenols.

Aromatic, or volatile, oils and stearoptenes are discussed elsewhere.

Cresol (Cresylic Acid, *Trikresol**).

Cresol is a mixture of phenols obtained during the distillation of coal tar. It occurs as a white or straw-coloured oily liquid with a smoky odour. In contrast to phenol, cresol is less toxic, but its antiseptic value is markedly reduced by organic matter. It is vaporised from a special lamp for the relief of whooping-cough and other respiratory disorders. As a disinfectant it is used in the form of lysol (*q.v.*).

Liquor Cresolis Saponatus, Off. (Lysol).

A solution of cresol with soft soap which forms a clear liquid on dilution with water. For general surgical purposes a dilution of one drachm to the pint of water may be employed; for infected linen and sickroom utensils an ounce to the pint is the usual strength. Poisoning by lysol should be treated by washing out the stomach with a strong solution of magnesium sulphate, which diminishes absorption, and the subsequent administration of liquid paraffin.

Phenol (Carbolic Acid), 1–3 gr.

Phenol is obtained from coal tar; it occurs as small, white crystals having a characteristic odour. For convenience it is often employed as *Phenol Liquifactum*, containing about 80% of phenol itself. Phenol is caustic in concentration; diluted, it is a powerful antiseptic and local anæsthetic by its action on protoplasm. Phenol coagulates protein, but its combination with the latter is a loose one, so penetration readily occurs. Its action is only slightly reduced by organic matter but very greatly diminished by dilution. It has no specific action against some bacteria more than others. Swallowed in concentrated form, as by suicides, it causes sloughing of the gastro-intestinal tract with shock collapse and usually death. Treatment should be on the same lines as with lysol. Taken internally, small doses (1–2 gr.) may check hypersensitivity of the gastric mucous membrane. As a 1% lotion it is employed to relieve pruritus, the irritation from insect bites, etc., and the same strength is used as a gargle and mouthwash, especially following tooth extraction, where it relieves after-pain. Combined (25%) with camphor or collodion it is used as a topical application against toothache. Phenol and camphor in equal parts, and triturated until liquefied, is a useful preparation in the treatment of dermatophytosis. A 5% aqueous solution is used to disinfect instruments, utensils, etc. The following is a useful palliative ointment for chilblains: phenol 1%, camphor 6%, balsam of Peru 2%, soft paraffin 25%, hard paraffin 7·5%, anhydrous lanolin to 100%.

Phenol lotion must not be used on wounds or over a large area of abraded skin, as it kills tissues in the same concentration as bacteria, and a white slough may be formed. Furthermore it is rapidly absorbed and readily gives rise to toxic conditions. These are characterised by renal irritation and albuminuria and damage to the central nervous system, the latter causing vomiting, weakness, coma, occasional convulsions and death by paralysis of the medullary centres.

Phenolic bodies are excreted in the urine conjugated with sulphuric and glucuronic acids; these products tend to darken the urine to a greenish or brown colour. Phenol burns on the skin should be washed with alcohol and then treated with oil. Phenol poisoning, internally, should be treated as in the case of lysol, *vide antea.*

Glycerinum Phenolis, Off.

Diluted with three or more parts of glycerin it is used to relieve the pain of *otitis media* and promote drainage of fluid through the tympanum.

Unguentum Phenolis, Off.

Contains 3% phenol and is used principally to relieve pruritus. It is also applied to parasitic skin conditions. The Pharmacopœia directs that this ointment should be supplied in collapsible tubes.

Resorcinol, 1–5 gr.

Resorcinol is a dihydroxyphenol, freely soluble in water. It was formerly used internally as an antipyretic, but, like many related substances, it may form methæmoglobin and cause collapse. Externally it is a more powerful antiseptic and less irritating than phenol; as a strong reducing agent it destroys aerobic organisms by depriving them of oxygen. Resorcin is used in solutions and ointments (2%–10%) in psoriasis, eczema, pruritus, etc., and in hair lotions for seborrhœa. By absorption of oxygen it forms a dark-coloured compound and may discolour fair hair.

Unguentum Resorcinolis Compositum, B.P.C.

A useful application for chronic eczema, cellulitis, *pruritus ani*, etc.

Hexyl-Resorcinol (*Caprokol**), 2–10 gr.

If this derivative of resorcinol be dissolved 1 in 1,000, in 30% glycerin, the solution has a very low surface tension and is used as a penetrative antiseptic for abrasions and wounds. The same solution diluted with two parts of water is employed for mucous surfaces. Dissolved in olive oil and administered in capsules, the drug has been used as a urinary antiseptic. It is used also as a contraceptive, and may be given internally to expel roundworms and threadworms.

Chlorinated Phenols

Chlorocresol.

Chlorocresol is a potent disinfectant possessing low toxicity, and is active in both acid and alkaline media. It is largely used, in a concentration of 0·1%, as a bacteriostatic in preparations for parenteral administration.

Chloroxylenol.

Chloroxylenol has the same properties as chlorocresol but is even more potent. It is very widely used in proprietary antiseptic preparations resembling the official preparation following.

Liquor Chloroxylenolis, Off. (Roxenol, *Pathone,** *Lysantol,** *Dettol,** *Neomonsol,** sim.).

An alcoholic, saponaceous solution containing chloroxylenol with terpineol, etc. It is used diluted with ten to forty parts of water as a surgical antiseptic.

Antiseptic Dyestuffs

Acriflavina (Flavine, Acriflavinæ Hydrochloridum).

Acriflavine is a powerful antiseptic, non-irritant and relatively non-toxic to the tissues; it does not affect phagocytosis and its activity remains unaltered in the presence of serum. It has the disadvantage of slowness of action. Acriflavine is especially valuable against staphylococcal infection. It is employed as a 1 : 1,000 solution for early application to infected wounds to prevent the spread of sepsis, and as a surgical antiseptic during operations. The emulsion is employed against burns, in the after-care of surgical cases for plugging discharging cavities, in obstetrics and in certain skin conditions such as pemphigus. Solutions in normal saline are unstable.

Emulsio Acriflavinæ, B.P.C., 1 : 1,000 in a water-in-oil emulsion.

Euflavina, ½–1 gr. (*Trypaflavin**).

Euflavine (or neutralised acriflavine) has similar properties to the above, but is even less irritant. It is, therefore, more suitable for intravenous injection, for oral administration, and in ophthalmology. It is given orally in "enteric" coated tablets or capsules for gonorrhœa and urinary infections generally. Intravenous injections have been used in septicæmic states, but modern chemotherapy has superseded this type of treatment. For bladder irrigation, etc., an average strength of 1 : 2,000 is employed. For pre-operative skin sterilisation and skin infections 1% in alcohol 70% is useful.

Carbasus Euflavinæ, B.P.C., Euflavine Gauze.

Proflavinæ Hemisulphas, Off.

This official salt is the most suitable "flavine" for all purposes and must be supplied or dispensed when "proflavine" is ordered.

Proflavinæ Sulphas (Diaminoacridine Sulphate).

Proflavine strongly resembles acriflavine in structure and antiseptic powers, but is completely compatible with normal saline solution. For intravenous injection it is, therefore, superior in convenience. It is sufficiently non-irritating to be used in solution with safety in the peritoneal cavity and to the brain tissue. From 1 : 1,000 to 1 : 500 is the strength of aqueous solution usually employed. Proflavine hemisulphate may conveniently replace the official proflavine sulphate as the former is very much more soluble in water. Proflavine oleate is employed as a 1% solution in liquid paraffin. Flavazole, a combination of proflavine and sulphathiazole, is less irritant than proflavine itself, and is effective against gram positive cocci and gram negative bacilli. It can be used in solution for irrigation of the conjunctiva or infected body cavities, or as a powder in which 2 parts of flavazole are mixed with 98 parts of sulphathiazole. This is used as a wound antiseptic and as a diluent for penicillin powder employed for local application.

Other aminoacridine (flavine) compounds recently introduced may prove of great value as surface antiseptics; one of them, the 5-aminoacridine analogue, is non-staining.

Methylthioninæ Chloridum, 1–5 gr.

Methylene blue is given by mouth, in pills or capsules, as a genito-urinary antiseptic, imparting a greenish colour to the urine. A dosage of 1 to 2 grains three times daily has been used with success in preventing the occurrence of cyanosis following sulphonamide administration. In cyanide poisoning, methylene blue intravenously (50 mils. of a 1% solution) has proved successful, probably by accelerating the tissue oxidation processes.

Potassii Hydroxyquinolini Sulphas (*Chinosol**).

A light yellow, water-soluble body which is used externally, 1 : 2,000–1 : 500, in mycoses and other infective conditions of the skin. Vaginal suppositories are prepared with potassium hydroxyquinoline sulphate for contraceptive purposes.

Chiniofonum, 1–8 gr.; rectally 15–75 gr. Off. (*Yatren**).

An iodised compound related to the above, which contains 20% of sodium bicarbonate. It is a mild intestinal antiseptic, and a specific against amœbic dysentery. For the latter, retention enemata containing up to 5% of the drug may be injected morning and evening. Solution is affected by the aid of gentle heat.

Diodoquin.

This iodised oxyquinoline compound is relatively non-toxic and it has established its utility in the treatment of amœbiasis. Occasional nausea or rashes may follow its use. The drug is given by mouth in doses of 9·6 gr. daily for two to three weeks and is combined with emetine and followed by carbasone therapy.

Rubrum Scarlatinum (Scarlet Red).

Ointments of various strengths from 2% to 8% are used to stimulate the granulation of clean ulcers and to regenerate skin.

Viola Crystallina (Crystal Violet, Methyl Violet, Medicinal Gentian Violet).

This purified form of methyl violet is a powerful antiseptic. It is used as a 5% solution in 20% alcohol as a paint for staphylococcal skin infections. Intravenously as a ½ to 1% solution (0·003–0·007 gm. per kilo. bodyweight) it is sometimes used against staphylococcal and other septicæmias, and in endocarditis. A 1% aqueous solution is often used in thrush and aphthous conditions. A 2% solution is used in ringworm. Internally, it provides a safe and effective therapy against threadworms. For children the dosage is ⅛ grain daily per year of age; for adults the dose is 1 grain thrice daily, before meals. It has also been recommended for gastro-enteritis.

Triple Dye Solution (*Triofase**).

This is an aqueous solution containing crystal violet 2%, brilliant green 1%, and euflavine 0·1%. It is a very effective astringent, antiseptic application in the treatment of burns, but should not be used on the face or fingers.

Liquor Tinctorium, B.P.C. (Bonney and Browning's Solution, Blue Paint).
A mixed dye solution for skin sterilisation.

Viride Nitens, Off.
Brilliant green has a similar antiseptic action to acriflavine. It is strongly bactericidal to the coli-typhoid organisms, and is used as a 1 : 1,000–1 : 2,000 aqueous solution, and as a 1%–2% ointment. One in 500 solution in spirit with 3% salicylic acid is employed against ringworm of the scalp.

The Halogens

Both chlorine and iodine possess antiseptic properties and are used medicinally in compounds from which they may be liberated readily.

Cetrimide (*Cetyltrimethylammonium Bromide*).
This is described as a synthetic detergent in which the alkyl radicle carries a positive charge. The aqueous solution is powerfully cleansing and disinfectant, very useful in preparing the skin for operation and cleaning burns and dirty wounds, *e.g.* after street accidents. Although incompatible with soaps and with protein, it appears to be effective in the presence of serum and is non-toxic. It is usually employed as a 10% dilution of the commercially prepared solution (*Cetavlon**).

Calx Chlorinata (Bleaching Powder).
Chlorinated lime, on account of the readiness with which it parts with free hypochlorous acid in contact with putrefactive material, exerts a powerful deodorant and disinfectant effect. It is used as a powder to disinfect sickroom utensils and excreta, and in the proportion of 0·25–0·5 part per million for the purification of contaminated drinking water. The addition of a minute amount of sodium thiosulphate subsequent to the use of hypochlorite will remove all disagreeable excess of chlorine, etc. In solution the compound is employed for application to foul ulcers, for nasal and vaginal irrigation and as a gargle in septic tonsillitis, but its alkalinity is rather irritant and it is better replaced by the more stable Dakin's solution (*v. infra*), which has identical properties. Either solution may be employed to destroy mustard gas.

Liquor Calcis Chlorinatæ cum Acido Borico, B.P.C. (Eusol).

Liquor Chlori, B.P.C.
A solution of chlorine gas; uses similar to above.

Gargarisma Chlori, B.P.C.
A solution of chlorine and its oxides; uses similar to above.

Liquor Sodæ Chlorinatæ Chirurgicalis, Off. (Dakin's Solution).
This is a solution of sodium hypochlorite containing boric acid. It is probably the best of the inorganic chlorinated solutions and is used diluted with ten to twenty volumes of normal saline solution in the Carrel-Dakin method of wound irrigation. Solutions of similar dilution are employed as gargles or sprays in acute infection of the throat and for foul external ulcers. The active chlorine-containing constituents liberated by this and related antiseptics combine with and dissolve necrotic tissues; in consequence the solution speedily loses potency and needs frequent replacement, as in the Carrel-Dakin "continuous" method. When Dakin's solution is diluted (10 to 20 times) for ophthalmic irrigation the final solution should be made isotonic with tear secretion (≡0·9% NaCl) otherwise it is very painful in use.

Solutions of sodium hypochlorite, prepared electrolytically and without the subsequent addition of boric acid, appear to retain their chemical activity longer than Dakin's solution. It must be remembered, however, that with a pH of 10·5 such solutions possess some ten times the degree of alkalinity of the official solution, and this may be clinically undesirable. *Milton Disinfectant** contains 1·01% of sodium hypochlorite.

Chloramina (Chloramine T).

Chloramine is a chlorinated organic body which acts as an antiseptic by the slow liberation of chlorine, and closely resembles the hypochlorites in action. Chloramine is freely soluble in water, and its aqueous solutions, being only mildly alkaline, are much less irritant than Dakin's solution; a 2% solution is sometimes used for continuous wound irrigation. For the mouth, throat, bladder and urethra a 0·5% solution suffices. Chloramine solutions in water are very stable.

Dichloramina (Dichloramine T).

Dichloramine is related chemically to the above, which it also resembles in antiseptic properties. It is insoluble in water, but dissolves in organic solvents and chlorinated paraffin. Such solutions are used in the packing of septic cavities where prolonged medication is obtained by the very slow liberation of chlorine from the oily solution.

Azochloramide.

This compound is N.N.dichlorazodicarbonamidine plus sodium tetradecyl sulphate. It is used for the irrigation of cavities, including tuberculous empyemata, and also as a wet dressing for wounds. For this purpose it is employed as 1 in 3,300 solution in an isotonic buffered saline solution. It should not be applied to mucous membranes.

Iodum

(see also Thyroideum)

Iodine occurs as a heavy, black, lustrous solid which gradually sublimes at room temperature, forming a purple vapour. It is used by inhalation of the vapour against colds, bronchial infection and phthisis. For internal use, the element has largely been replaced by iodides, but it is still employed to prevent and cure simple goitre, and in toxic goitre, usually for a short period prior to surgical removal of the gland, when it effects a transient remission of the symptoms of hyperthyroidism. It appears to be of value in cases of failing lactation from the fourth day of the puerperium onwards. Lugol's solution is the preparation now mostly employed for internal administration.

Liquor Iodi Aquosus, Off. (Lugol's Solution), 5–15 min.

Lugol's solution contains iodine dissolved in an aqueous solution of potassium iodide. It is very stable, and is probably the most suitable preparation for oral administration. It may be given in milk.

Liquor Iodi Fortis (Iodine Liniment), Off.

This is used externally on unbroken skin as a counter-irritant and parasiticide.

Liquor Iodi Mitis, Off. 5–30 min. (Tincture of Iodine).

Weak solution of iodine is supplied when tincture of iodine is ordered on a prescription. It is used internally, and externally as a first-aid measure of antisepsis, and to sterilise skin prior to operation. It is also applied in mycotic skin diseases. It may give rise to dermatitis. In hospital practice for external purposes it is usually replaced by a 2% solution of iodine in acetone-free industrial methylated spirit.

Liquor Iodi Simplex, B.P.C. 5–10 min. (French Tincture of Iodine).

A chemically unstable solution used internally, usually in milk. The following is a useful paint to treat the bald spots of alopœcia:

℞ Ac. Salicyl .. .. .. gr. xv
Liq. Iodi Simp. .. .. ad ℥i
ft. pigment. pro app.

Oleum Iodisatum (_Neohydriol,_* _Lipiodol,_* _Iodatol_*).

An oily solution containing 40% of combined iodine, it is used as a contrast medium in radiography of the chest for diagnosis of bronchiectasis and bronchial obstruction, and for the accessory nasal sinuses. It may be used internally when inorganic preparations of iodine disagree.

Ethyliodophenylundecylate (*Myodil**).

This substance is used as a contrast medium in the radiological diagnosis of spinal cord tumours.

Iodoxylum, Off. (*Uroselectan B,* Pyelectan,* Uropac**).

This is a diodo-pyridone compound and contains about 50% of iodine. It is a white crystalline solid. It is used as a contrast medium for excretion pyelography, in doses of 10–15 gm. dissolved in 20 ml. of distilled water. The solution, warmed before use, must be slowly injected intravenously. In weaker solution, it can be used for retrograde pyelography. Contraindications are acute nephritis, renal and hepatic failure, and severe general disease.

Injectio Diodoni, Off. (*Diotrast,* Pyelosil**).

This diodo-pyridone compound contains iodine, and is a clear liquid. It is used as a contrast medium for excretion pyelography and cholecystography, as well as in arteriography, where it has largely replaced thorium dioxide (*Thorotrast**). The dose is 20 ml.; for children 8–10 ml.; for infants 2–3 ml. The contraindications are the same as for iodoxylum.

Pheniodol.*

This is an organic complex containing a high proportion of iodine. It is administered by mouth as a contrast medium in cholecystography, and there is evidence that it may prove superior for this purpose to iodophenolphthalein (*q.v.*) administered orally. The adult dose (3 gm.) is given as an aqueous suspension containing mucilage. ***Pheniodol Meal, B.D.H.**** contains pheniodol with suitable suspending and flavouring agents, ready for admixture with water.

Pigmentum Iodi Compositum, B.P.C.

Mandl's paint is a glycerinated solution of iodine and potassium iodide used as a stimulating antiseptic to the gums and throat.

Unguentum Iodi Denigrescens, B.P.C. (*Iodex**).

Non-staining iodine ointment is a suitable preparation for external application to inflamed joints, chilblains, enlarged glands, etc. It may be prescribed with 5–10% of methyl salicylate (*q.v.*) added for the treatment of fibrositis, etc.

Colloidal iodine is available in various forms as trade specialities. It is prepared for internal use, for injection, and as an external application. Its especial value is doubtful. Other organic iodine compounds intended for internal administration as alternatives to the iodides are *Iodicin,* Iodoprotein,* Iodostarin,* Lipoiodine,** and *Seroden.**

U.F.I. (*q.v.*).

The Iodides

The commonest iodides in use are those of potassium, sodium and occasionally calcium. The general properties of these salts are similar to those of potassium iodide. Iodides are added to table salt in endemic areas as a prophylactic measure against simple goitre. See also under Iodine.

Potassii Iodidum, 5–30 gr.

The actions of potassium iodide, although valuable in treatment, are largely empirical in basis. The salt is used in the later stages of syphilis in doses of 15–30 gr. three times daily to promote the resolution of syphilitic granulation tissue and so render the spirochætes more accessible to the arsenicals, bismuth, etc. It is also used empirically in arteriosclerosis, fibrositis, rheumatoid arthritis and bronchial asthma. Its use an an expectorant is discussed elsewhere. Large doses (up to 60 gr. four times daily) are given in actinomycosis and other fungus diseases. It is best administered together with sodium bicarbonate, as the liberation of some free iodine may occur in an acid stomach. If it causes gastrointestinal upset the dose can also be dissolved in a small quantity of water and given in milk. It may give rise to a feeling of depression, and this may be partly overcome by administering it with nux vomica. It is given to promote the absorption of serous exudates, and also in chronic lymphadenitis but on very scanty evidence of real clinical improvement. Idiosyncrasy is evidenced by copious nasal and bronchial secretion, and skin rash, which may be papular, vesicular, pustular or purpuric.

Sodii Iodidum, 5–30 gr.

The action and uses of sodium iodide are similar to those of the potassium salt. A sterile solution (15–30%) is used in retrograde pyelography as a contrast medium. In syphilis the drug is sometimes given intravenously, 150 gr. in 100 ml. distilled water every 48 hours, for 20 to 30 injections. A small test dose should be given initially by mouth to test for intolerance.

Iodoformum, ½–3 gr.

Iodoform occurs as a yellow, insoluble powder with a characteristic odour. It is a non-irritant antiseptic; taken by mouth it is decomposed with the liberation of iodine, and it has been used against intestinal infection and as a tænicide, but dangerous toxic sequelæ, including respiratory paralysis, may occur. Applied externally to syphilitic and other ulcers, and septic wounds, it exerts a mild anæsthetic action; the antiseptic effect is produced by slow liberation of iodine.

Carbasus Iodoformi, B.P.C. (Iodoform Gauze).

Used for plugging septic cavities after operation.

Pasta Bismuthi et Iodoformi, B.P.C. (B.I.P.P.).

Bismuth subnitrate, iodoform and paraffin, a stiff paste used with gauze for packing septic cavities.

Pigmentum Iodoformi Compositum, B.P.C. (Whitehead's Varnish).

Used as an antiseptic external application.

Suppositorium Iodoformi, Off.

For the relief of pruritus, and useful in anal fissure.

Oxidising Antiseptics

Chromii Trioxidum (Chromic Acid).

Chromium trioxide is a powerful oxidising antiseptic which is used in solution for topical application. It is used as a gargle (1 : 500), in septic tonsillitis and for oral sepsis. For nasal and vaginal irrigation a 1 : 2,000 solution is suitable. It is applied as a paint (25%) to destroy condylomata and warts, and for lupus. A 2½% solution is used as a paint to ulcerations of the gums and in periodontitis. To relieve bromidrosis a 5% lotion may be employed. Idiosyncrasy to chromium applications is not uncommon.

Gargarisma Chromii Trioxidi, B.P.C. (0·2%).

Liquor Hydrogenii Peroxidi, Off. ½–2 fl. dr.

Solution of hydrogen peroxide owes its antiseptic action to the liberation of nascent oxygen in contact with tissue peroxidases. The official solution contains approximately 6% of H_2O_2; it is termed "20-volume" peroxide, which means that the available oxygen in one volume of the solution would occupy, on liberation, twenty volumes at N.T.P. It has occasionally been given by mouth against flatulent dyspepsia, but its principal use is as a topical antiseptic for septic wounds, and foul ulcers. The solution may be employed diluted with three volumes of normal saline as a paint to septic gums and to mucous surfaces generally, but, after use, rinsing with normal saline is recommended. A 1 : 20 dilution is a commonly employed mouthwash. It is mildly hæmostatic and may be employed, diluted, to abrasions, etc., for this purpose and to lessen risk of infection. Its use is undesirable after extraction of teeth, as septic matter may be forced into the cavity by the pressure of the released gas. Insect stings are speedily relieved by application of the diluted solution on a pledget of wool. In otorrhœa a dilution of one part of the official solution and three parts of water is used as ear drops; after a few minutes a few drops of industrial methylated spirit are added to assist in drying the meatus. This use of peroxide is, however, condemned as dangerous by some otologists. Instilled into the ear it loosens hardened cerumen. The official solution (20 volume) is useful when diluted for removing adherent surgical dressings, partly by its solvent effect on clotted blood and partly by the mechanical action of the nascent oxygen liberated, in gently pushing the dressing away from the wound. Applied undiluted to the epidermis, the official solution (20 volume) causes transient bleaching and pruritus.

Magnesii Peroxidum, ½–1 dr.

A tasteless, insoluble powder liberating oxygen after ingestion. Used orally against flatulence, and infections of the alimentary tract; also as a component of oxygenated dentifrices.

Zinci Peroxidum.

A cream containing zinc peroxide was devised for the plugging of empyema cavities, and the preparation has been used also for application to varicose ulcers, etc. The beneficial effect is apparently due to the slow liberation of nascent oxygen, and possibly the zinc ion. The cream devised at Brompton Hospital is as follows:

Zinc peroxide (absolute) ..	10
Glyceryl monostearate ..	3
Arachis Oil	to 100

Potassii Chloras, 5–10 gr.

Potassium chlorate is a mild antiseptic. It is used principally in 2% solution as a gargle against tonsillitis and as a mouthwash in stomatitis and gingivitis. Taken by mouth it is absorbed and excreted into the bronchi and in the saliva, and is used in bronchitis and tonsillitis, especially of children. It is contraindicated where renal damage exists, and given over a long period methæmoglobinæmia and collapse may supervene.

Potassii Permanganas, 1–3 gr.

Potassium permanganate oxidises organic matter, and is, therefore, antiseptic and deodorant. Internally in " enteric " coated tablets it is used against cholera. As a mouthwash and mildly astringent gargle, solutions 1 : 5,000 (preferably in normal saline) are used; for bladder, urethral and vaginal irrigation 1 : 10,000. It is a useful antidote in morphine, phosphorus, and cocaine poisoning, when used for gastric lavage as a 0·3% solution it destroys any of the poison remaining in the stomach. In the treatment of snake-bite the area is freely and deeply incised and potassium permanganate, in powder form, rubbed into the wound. In cases of extensive skin sepsis, including confluent smallpox, bathing with a weak solution (about 5 gr. to a bath) of potassium permanganate is useful. *Condy's Fluid** is a solution containing sodium permanganate.

Intestinal Antiseptics

Many attempts have been made to devise effective antiseptics to destroy pathogenic bacteria in the intestine, but with indifferent results prior to the introduction of suitable sulphonamides (*q.v.*). The following are occasionally used:

Aromatic Oils and Stearoptenes (*q.v.*).

Betanaphthol (Naphthol), 5–10 gr.

Betanaphthol is administered as a tablet, powder or cachet, in enteric fever, cholera, flatulent distension of the bowel, and as a vermifuge. It is contraindicated in kidney disease. Exernally, as Kaposi's ointment, it is useful for scabies and psoriasis.

For Internal Use

℞	Betanaphthol	gr. v
	Carbo. Lig.	gr. viii
	fiat oblatum.	pro dos.

Kaposi's Ointment (Modified)

℞	Betanaphthol	12%
	Calc. Carb.	10%
	Sapo Moll. Adipem	āā ad ℥i
	fiat unguentum.	

Bismuthi Salicylas (*q.v.*).

Carbo, 1–2 dr., **Kaolinum**, ½–2 oz.

Charcoal and kaolin (*q.v.*) are not chemical antiseptics, but they exercise the physical action of adsorbing intestinal toxins, hence are of value in infective diarrhœas. This holds true particularly for kaolin, which is a form of aluminium silicate. It is a finely divided, insoluble powder which, in sufficient dosage, provides a protective coating to the gastro-intestinal mucosa and helps to lessen irritation. Charcoal in fine powder is sometimes used in flatulent dyspepsia to adsorb gas. *Allisantin*,* a compound of garlic and activated charcoal, has been used in conditions of diarrhœa.

Creosotum, 2–10 min.

Creosote is obtained by the destructive distillation of beechwood; it contains the phenol **Guaiacol**. Creosote exerts an antiseptic action, and is used internally and by inhalation for pulmonary tuberculosis, bronchiectasis, and fœtid bronchitis. It is used also as an intestinal antiseptic, especially in the treatment of arthritis, and occasionally in ointment form for external application. Creosote is liable to derange digestion and irritate the stomach. It is better, therefore, to prescribe guaiacol carbonate, which is tasteless and passes through the stomach unchanged to be partly hydrolysed in the intestine with the liberation of free guaiacol. *Resyl*,* containing glycero-guaiacol-ether, and *Cresival** (calcium cresol sulphonate) are expectorant preparations.

Fel Bovini (Ox-bile) (*q.v.*).

Hexamina (*q.v.*).

Salol (Phenyl Salicylate), 5–20 gr.

Salol passes through the stomach unchanged, but is partly hydrolysed in the intestine to form phenol and alkali salicylate. On this account it is employed to diminish intestinal putrefaction, but the action is very slight. It is contraindicated when renal inflammation exists. Salol is insoluble in water, but it may be prescribed in suspension, usually with a bismuth mixture, in cachet form, or as tablets, which should be chewed before swallowing.

Mercurial Preparations

The soluble mercuric salts used in medicine differ from those of other heavy metals in being rapidly absorbed and, in therapeutic concentrations, exerting no astringent action on living tissues. This is due to two reasons: the ionised salts, like mercuric chloride, precipitate protein, as do other metal salts, but the precipitate is soluble in the excess of protein which is invariably present owing to the small concentration of the mercuric ion used in actual therapy. Other mercurials, such as the oxycyanide, yield few free ions, hence are non-astringent. As antiseptics, however, many mercurial preparations suffer from the dual disadvantage of being greatly diminished in activity by the presence of organic matter, the latter tending to adsorb the mercury and so prevent it acting on the bacteria, and of being readily absorbed and producing systemic toxic effects when applied to body cavities, wounds, etc. Apart from its general antiseptic properties, mercury has long been used in the treatment of syphilis because of its specific action on the causal organism. In syphilis it is now almost always employed in conjunction with arsenic and bismuth therapy. For an account of the aperient and diuretic actions of mercury the appropriate sections should be consulted.

Hydrargyrum.

Metallic mercury, minutely subdivided, is used internally as *Hydrargyrum cum Creta*, Off. (*q.v.*), and *Pilula Hydrargyri*, Off., 4–8 gr., for its aperient, diuretic and antisyphilitic actions. As *Unguentum Hydrargyri*, Off., it is employed by inunction into the muscles against syphilis. Ointments containing 10% of metallic mercury are used to destroy parasites, *e.g.*, *pediculosis pubis*, but may produce dermatitis.

Injectio Hydrargyri, B.P.C. 5–10 min.

An oily suspension of metallic mercury intended for intramuscular injection in the treatment of syphilis.

Unguentum Hydrargyri Compositum, Off. (Scott's Dressing).

This is applied on lint in bursitis, tenosynovitis, etc.

Unguentum Hydrargyri Nitratis Dilutum, Off.

An active stimulating and anti-parasitic ointment widely used in dermatology. Applied in the early stages it may prevent the development of furunculosis.

Hydrargyrum Ammoniatum (White Precipitate).

This insoluble white powder is an amino-mercuric chloride. It is more active in ointment form than the oxides of mercury for the treatment of pediculosis, impetigo, scabies, ringworm and parasitic skin diseases generally, and is less liable to produce dermatitis than ointments containing metallic mercury. The ointment acts better than aqueous solutions of soluble mercuric salts in pediculosis because the fatty base tends to obstruct the breathing apparatus of the parasites. When intended to cover a large area the official ointment should be diluted with one or more parts of soft paraffin to minimise risk of a toxic dose being absorbed. It is often admixed with zinc oxide ointment in the treatment of chronic eczema. The following is a useful application for the purpose:

℞ Ol. Cadini 10%
Ung. Hyd. Ammon. } āā p. æq. ad ℥i
Ung. Zinc. Oxid. .. }
ft. ung. pro applicatio.

Unguentum Hydrargyri Ammoniati, Off.

Hydrargyri Iodidum Rubrum, $\frac{1}{32}$–$\frac{1}{16}$ gr.

Red mercuric iodide is insoluble in water, but dissolves in solution of potassium iodide, forming a double salt which is preferred as a surgical antiseptic to the perchloride, since in dilute solution it is less irritant to the skin, does not corrode steel or plated instruments, and does not precipitate with hard tap-water. Externally, the salt is stimulant, and is occasionally used as a vesicant; the B.P.C. ointment is a suitable application for *lupus vulgaris*, dermatophytosis and syphilitic sores. Ethereal Antiseptic Soap (surgical liquid soap) is medicated with 0·05% of the salt with potassium iodide. Solutions of mercuric iodide (with potassium iodide) are variously employed in surgical practice, 1:5,000–1:2,000 for wounds, and 1–1,000 for skin sterilisation. For vaginal irrigation 1:10,000–1:5,000 is suitable.

Liquor Saponis Antisepticus, B.P.C.

Antiseptic ethereal soap is used for surgical cleansing, it contains red mercuric iodide.

Unguentum Hydrargyri Iodidi Rubri, B.P.C.

A 4% ointment used as suggested above.

Hydrargyri Oxidum Flavum.

Yellow oxide of mercury possesses the general properties of the insoluble mercurials which slowly yield ions in contact with living tissue. In lotion form the oxide is applied to syphilitic sores, while ointments of various strengths up to 10% are used against venereal eruptions and chronic skin diseases.

Lotio Hydrargyri Flavum, B.P.C. (Yellow Wash).

Oculentum Atropinæ cum Hyd. Oxid., Off.

Oculentum Hydrargyri Oxidi, Off.

This is used for the treatment of inflamed eyelids, styes, etc.

Hydrargyri Oxycyanidum.

Mercuric oxycyanide is a powerful, non-ionising antiseptic. The following strengths of aqueous solution are used:

1 : 500	*Ophthalmia Neonatorum.*
1 : 5,000–1 : 1,000	Conjunctivitis.
1 : 10,000–1 : 5,000	Bladder Irrigation and Urethral Injection.
1 : 300–1 : 200 ..	For wounds and surgical instruments.

Hydrargyri Perchloridum, $\frac{1}{32}$–$\frac{1}{16}$ gr.

The introductory remarks concerning ionising mercuric salts are especially exemplified by mercuric chloride. In aqueous solution the following are suitable strengths for the purposes specified:

1 : 1,000	For pre-operative skin sterilisation and in bacterial infection. Also for ringworm of scalp.
1 : 100,000–1 : 10,000	As a surgical antiseptic for minor wounds.
1 : 10,000–1 : 5,000	Eye lotions, urethral injection.
1 : 2,000	Against pediculosis.

The following paint is effective in ringworm: mercuric chloride 1%, salicylic acid 9%, phenol 10%, and glycerin 80%.

For internal use against syphilis, the salt is best administered in combination with potassium iodide.

For tertiary manifestations of syphilis:

℞	Liq. Hyd. Perchlor.	ʒss
	Potass. Iodid.	gr. x
	Aq. Menth. Pip.	ad ℥ss
	ft. mist.	pro dos.

Liquor Hydrargyri Perchloridi, Off. ½–1 fl. dr.

Hydrargyri Subchloridum, ½–3 gr. (Calomel).

The uses of mercurous chloride as an aperient and diuretic are referred to in the appropriate sections. In ointment form it is used as a prophylactic against syphilitic infection, and for application to the primary sore. The ointment is also a useful application for impetigo, pediculosis, eczema and pruritus. In these conditions the official ointment should be diluted with an equal proportion of soft paraffin if the affected area is at all widespread.

Injectio Hydrargyri Subchloridi, B.P.C. 10–20 min.

An oily suspension used for intramuscular injection against syphilis. It may cause pain.

Lotio Hydrargyri Nigra, B.P.C. (Black Wash).

An aqueous lotion for application to the primary sore of syphilis.

Unguentum Hydrargyri Subchloridi, Off.

*Merthiolate** (Sodium ethylmercurisalicylate).

This contains 10% of mercury in organic combination and is less toxic than mercury perchloride. It is an effective antiseptic for sterilising tissue surfaces. As a surface antiseptic and for sterilising instruments it is used in 1 in 1,000 solution, whilst for mucous membranes 1 in 2,000 to 1 in 5,000 solution, and for bladder or ocular irrigation 1 in 5,000 solution is employed. It is also used in a cream base (1 in 1,000) for mycotic and acneiform skin infections, and as a suppository (1 in 1,000) for vaginal infections.

Phenylhydrargyri Nitras.

Phenylmercuric nitrate is a powerful germicide of low toxicity. It is non-irritant to the tissues and exerts a bacteriostatic effect even in extreme dilutions. Except for internal use it may with advantage replace mercuric chloride in all cases where a mercurial antiseptic is required. The following strengths of aqueous solution are suitable for the purposes named:

1 : 3,000–1 : 1,500	For application to wounds and skin sterilisation.
1 : 30,000	For urethral and vaginal irrigation and as an eye lotion.
1 : 2,000–1 : 1,000	Against epidermophytosis.
1 : 5,000	For irrigation of empyema cavities, particularly tuberculous ones.

Instead of a solution, phenylmercuric nitrate is often used as an ointment in a water-soluble base. It is added to preparations for parenteral injection as a bacteriostatic and is employed in suppository form as a contraceptive.

Phenylmercuric Chloride and Phenylmercuric Acetate.

These compounds are used for mycotic skin infections. An ointment in a vanishing-cream base, an aqueous solution not exceeding 0·25%, or an adhesive lotion with calamine not exceeding 0·5% can be employed.

Mercurochromum, B.P.C. (di-sodium di-bromohydroxy-mercuri-fluorescein).

A non-irritant antiseptic containing approximately 0·25% of mercury. It is used as a 1 to 2% solution for irrigation of the bladder, ears, eyes, etc. It is no longer used intravenously.

Mercury Sulphide.

A 1% colloidal solution (*Collosol mercury sulphide**) is used in the treatment of syphilis and psoriasis. Oral dose: 1 to 2 drachms. Intramuscular injection: 1 to 5 ml., toxicity is claimed to be low.

Metaphen.*

This is the anhydride of 4-nitro-5-hydroxymercuri-o-cresol. It is a germicide stated to be about ten times more potent than mercuric chloride. It is used as a 1 in 2,500 aqueous solution of the sodium salt for disinfection of surgical instruments and is stable and non-corrosive. It is also employed in similar concentration as a local antiseptic for wounds, genito-urinary, ocular and nasopharyngeal infections.

Mercurial Poisoning and its Treatment

Acute (Mercuric Chloride, etc.).—Corrosive action on alimentary tract causing vomiting, diarrhœa and collapse. Later severe renal damage occurs with albuminuria and hæmaturia; suppression of urine and death from uræmia may also follow.

Treatment: Any of the following may be given by mouth. Powdered charcoal, white of egg, sodium bicarbonate, tannic acid, follow this by thorough gastric and colonic lavage, preferably using a 5% solution of sodium formaldehyde sulphoxylate, an efficient chemical antidote to mercuric chloride. An emetic is less efficacious. Systemic treatment consists in the slow intravenous injection of 200 mls. of a 10% solution of a sodium formaldehyde sulphoxylate. Sulphydryl (–SH) compounds diminish the toxicity of mercury salts and the most effective in this respect is British Anti-Lewisite (BAL), which has been shown to be a good antidote in mercury poisoning (*q.v.*).

Chronic.—Chronic poisoning may arise in subjects undergoing prolonged mercurial therapy for syphilis. It is characterised by salivation, stomatitis, gingivitis (with blue line of mercuric sulphide), loss of weight and albuminuria. Industrial operatives exposed to mercury vapour may, in addition to the above, display nervous symptoms such as tremor, paralysis and insanity.

Urinary Antiseptics

Acidum Benzoicum (*q.v.*).

Acidum Mandelicum.

The advent of the mandelic-acid treatment of genito-urinary infection represented an important advance in this branch of drug therapy. Mandelic acid, administered as sodium mandelate, appears unchanged in the urine, and if the urine be maintained at or below pH 5·3, decided clinical improvement follows its use, especially in *B. Coli* infection. The original method was to administer sodium mandelate in 60-gr. doses and to maintain the appropriate reaction of the urine by the simultaneous administration of ammonium chloride in capsules or cachets. A later development has been to exhibit the acid as ammonium mandelate in the form of a mixture or elixir (*e.g. Mandelix**), and this usually obviates the need of additional ammonium chloride, since the ammonia is excreted as urea, leaving the mandelic acid free to acidify the urine (*cf.* ammonium chloride). The treatment is adaptable to young infants as well as to adults.

Mandelate therapy is most effective in *Bacterium Coli* and enterococci infections. It is necessary to restrict fluid intake to 2 pints daily to ensure adequate mandelate concentration in the urine. Also the urine should be tested each morning for acidity, using methyl red. The indicator should give a pink, not a yellow, colour. Mandelates are contraindicated in cases of renal failure and are usually ineffective in cases of obstruction to urinary flow. Mandelate therapy is a useful alternative to sulphonamide treatment of urinary infection in cases which have become drug-fast to the latter group.

Mistura Ammonii Mandelas, N.W.F. Dose: ½ fl. oz. (≡3 G. mandelic acid).

Calcii Mandelas. Dose: 3·5 G. four times daily (*Mandecal,** sim.).

Calcium mandelate appears to be as effective as ammonium mandelate in acidifying the urine (*cf.* calcium chloride), and it is more pleasant to take and less irritating to the gastric mucosa. Occasionally concurrent ammonium chloride is necessary to achieve appropriate urinary acidity. Methenamine mandelate is a recently developed compound of greater potency.

Acriflavina—Proflavina (*q.v.*).

Benzoates (*q.v.*).

Buchu (a leaf).

Buchu leaves contain an aromatic oil which exerts a mildly antiseptic action in the urine. It is used principally as *Infusum Buchu,* 1–2 fl. oz., as a vehicle in mixtures. The following is a suitable sedative preparation in acute and subacute cystitis:

℞	Potass. Acet.	gr. xxx
	Tinct. Hyoscy.	♏xx
	Sp. Chlorof.	♏v
	Inf. Buchu	ad ℥i
	m. ft. mist.	pro dos.

Hexamina, 10–30 gr.

Hexamine should be taken well diluted to minimise any local action in the stomach following liberation of formaldehyde by the gastric acid. It is excreted by the kidneys and, in acid urine, traces of formaldehyde are liberated. It is useful in pyelitis and cystitis and to sterilise the urine of typhoid carriers, sodium acid phosphate or ammonium chloride being administered concurrently to ensure the acidity of the urine. The liberation of formaldehyde in an acid urine may not, however, be the sole mode of action, as hexamine itself has some bacteriostatic action. It is used in cholecystitis in dosage as large as 300 gr. daily provided that sodium bicarbonate or acetate is administered concurrently in sufficient dosage to keep the urine alkaline. Although hexamine appears in the cerebrospinal fluid it is probably useless in inflammatory conditions of the central nervous system. When excreted in an acid urine, hexamine may, in susceptible subjects, give rise to severe hæmorrhagic cystitis. Hexamine is excreted in the biliary tract, and a preparation, *Felamine,** a compound of hexamine and cholic acid, is sometimes given in infections of the biliary tract. *Cystopurin** is hexamine sodium acetate. **Formamol** (*Helmitol**) is hexamine anhydromethylenecitrate.

Hexyl-resorcinol (*q.v.*).

Methylthionina (Methylene Blue, *q.v.*).

Oleum Santali, 5–15 min.

Sandalwood oil is very occasionally administered in capsules in the treatment of gonorrhœa and gleet, chronic cystitis and urinary infection generally, especially that of staphylococcal origin. It is diuretic (see Volatile Oils) and mildly antiseptic.

Penicillin (*q.v.*).

Liquor Santali Compositus, B.P.C., 1–2 fl. dr.

Sulphonamides (*q.v.*).

These are the most important of urinary antiseptics.

Miscellaneous Antiseptics

Acidum Boricum, 5–15 gr.

Boric acid is a mild antiseptic of little real utility. Internally it is unsafe, its excretion is slow and there is danger of poisoning, through cumulation. Externally in 3% solution it is used to wash wounds and ulcers, and for the irrigation of cavities after operation. In combination with starch and/or zinc oxide it is used as a mildly desiccant dusting powder. For bladder irrigation, etc., a 2% aqueous solution is employed.

Collyrium Acidi Borici, B.P.C. (Boracic Eye Lotion).

Contains 2% of boric acid and is used neat or diluted with an equal proportion of hot water. Zinc sulphate (¼%) is often added.

Linteum Acidi Borici, B.P.C. (Boric Lint).

Unguentum Acidi Borici, Off.

A harmless, emollient ointment.

Formaldehydum.

Formaldehyde is used as the official **Liquor Formaldehydi** (Formalin), which contains about 40% of formaldehyde itself. It is a powerful disinfectant used for sterilisation of skin, surgical instruments, etc., but it is highly irritant to mucous membranes. If very carefully applied undiluted to ringworm patches, one application may suffice for a cure. As a nasal spray for ozœna 1% in normal saline is used. A strength of 1 : 500 is suitable as a mouthwash. Gelatin exposed to the action of formaldehyde may pass through the stomach undigested, and this formalinated gelatin is often employed to replace the older forms of " enteric " coating for pills, tablets and capsules. For disinfection of rooms it is usual to vaporise paraformaldehyde, an isomer, from a special lamp. Plantar warts can be treated by the application of 3% formalin for 10 minutes nightly. The treatment of ringworm by iontophoresis with 1% formaldehyde is of value. Foot baths are useful for hyperidrosis.

Acidum Picricum (Picric Acid, Trinitrophenol).

This is used in 1% aqueous or alcoholic solution for pre-operative skin sterilisation. It should not be applied to large burns or wounds as absorption may occur with toxic renal irritation, etc. A paint containing 2% of picric acid, 50% camphor and 48% alcohol is used against ringworm of the scalp.

Phemeride.*

This compound is *p*-tertiary-octylphenyldiethoxybenzyldimethyl ammonium chloride. It is a bactericidal substance particularly effective against gram positive cocci, and is used as a surface antiseptic. It is also a detergent. It has the advantages of not harming the tissues and leucocytes to any extent, nor does it induce skin sensitivity.

Phenoxetol.*

This is ethyleneglycol monophenyl ether. It is non-irritant and is used as a wound antiseptic. Its antibacterial activity is pronounced against gram negative bacilli, particularly *Ps. pyocyanea.* It is a colourless, odourless liquid, and is used in concentrations not exceeding 2·2%. Not more than 1 oz. of this diluted solution should be applied as a single dressing.

Tetmosol* (Tetra-ethylthiuram).

A 5 to 20% concentration of this substance, made up with soap solution, is an effective prophylactic and curative agent against scabies.

Sodium Caprylate.

This fatty acid compound is claimed in America to be very effective in the treatment of ringworm of the feet. It is used as a 10% ointment. It appears to be superior to other methods of treatment, including such recently introduced compounds as propionate-propionic acid and undecylenate-undecylenic acid, the latter used as a 10% ointment or as the following powder: undecylenic acid 2%, zinc undecylenate 20%, in talc.

Oleum Chaulmoogræ.

Dosage: By mouth, 5 minims slowly increased to 60 minims.
By injection (subcutaneous, intramuscular), 30 minims slowly increased to 75 minims.

Chaulmoogra oil is mostly known in connection with the treatment of leprosy, but recently it has been successfully used as a local application in tubercular laryngitis. In leprosy the oil is applied locally, taken by mouth, or injected subcutaneously or intradermally into leprous lesions, usually mixed with an equal bulk of olive oil. The oil is supposed to penetrate the wall of the leprosy bacillus, thus rendering it more vulnerable, and at the same time to stimulate leucocyte activity. Chaulmoogra oil has been replaced almost entirely by. hydnocarpus preparations (*vide infra*).

Oleum Hydnocarpi.

Hydnocarpus oil has action and uses similar but superior to those of chaulmoogra oil (*q.v.*). It has the same range of dosage.

Oleum Hydnocarpi Æthylicum, Off.

The ethyl esters of hydnocarpus oil are similar in action and dosage to hydnocarpus oil, to which, however, they are preferred.

*Mycil.**

This preparation has been recently introduced as a fungicide. Chemically it is *p*-chloro-phenyl-a-glycerol ether.

Empyreumatic Substances

Empyreumatic, or tar-like, bodies are obtained by the destructive distillation of various organic substances. They are highly complex in chemical composition and are employed mainly for their stimulant, antiseptic and antipruritic action when applied to the skin.

Creosotum (*q.v.*).

Ichthammol, 5–10 gr. (*Ichthyol**).

Ichthammol is a sulphonated, tar-like substance derived from bituminous schists, containing the fossilised remains of fish, etc. It reduces inflammation and is antiseptic when applied externally, and is used in the treatment of acne, eczema and other chronic skin diseases, and in acute dermatitis. In erysipelas, a paint consisting of 25–75% of ichthammol with glycerin or water may be applied under a dressing. For urethral and vaginal irrigation an aqueous 2% solution is suitable. Internally, ichthammol is administered in pill form in the treatment of chronic skin diseases.

Glycerinum Ichthammolis, B.P.C.

Contains 10% of ichthammol.

Suppositorium Ichthammolis B.P.C.

Unguentum Ichthammolis, B.P.C.

Ichthammol, 10%, in a mixture of wool fat and soft paraffin.

Unguentum Ichthammolis Compositum, B.P.C.

Other ingredients, besides ichthammol, are sulphur, zinc oxide, resorcinol and salicylic acid. It is used in the treatment of acne and chronic eczema.

Oleum Cadinum.

Oil of cade is a mixture of substances obtained by the destructive distillation of a species of juniper. It is applied in ointment form as a stimulating antiseptic. The following is suitable for chronic eczema, etc.:

℞	Ol. Cadin.	4%
	Zinc. Oxid.	10%
	Sulphur	5%
	Adeps Lanæ Hyd.	20%
	Paraff. Molle	ad ℥i
	fiat ung.	pro app.

Pix Carbonis Præparata, Off.

Prepared coal tar consists of the residue after the more volatile constituents have been driven off by heating crude coal tar. Some dermatologists insist, however, that better results are obtainable with the crude substance, especially in cases of chronic eczema where the skin is much thickened (lichenification) and in psoriasis. In such conditions the tar is sometimes applied to the skin as a varnish, being removed after some days with the aid of grease. Generally, however, coal tar is used in ointment form (2%–5%) and is stimulant and antipruritic. Coal tar should not be employed when the skin is acutely inflamed, and prolonged use is undesirable since it has carcinogenic properties.

Liquor Picis Carbonis, Off. (Liquor Carbonis Detergens,* sim.).

This, when diluted with water (1 : 200), is used as an antiseptic, vaginal douche; a 1%–2% lotion is employed to relieve pruritus.

Pasta Picis Carbonis, B.P.C.

Crude coal tar, 3·5% in zinc paste.

Unguentum Picis Carbonis Compositum, B.P.C.

Solution of coal tar, and ammoniated mercury in soft paraffin.

Pig. Olei Picis cum Iodo, B.P.C.

This preparation is used for ringworm of the scalp.

Pix Liquida, Off. 2–10 gr. (Stockholm Tar).

This is obtained by the destructive distillation of the wood of the Scotch fir. Applied locally, its properties are similar to those of coal tar, but it is stated to be less effective for the relief of pruritus. Taken by mouth, certain of the antiseptic constituents are absorbed and appear in the bronchial secretion; it is, therefore, administered to relieve the cough of chronic bronchitis and phthisis.

Syrupus Picis Liquidæ, B.P.C., 1–2 fl. dr.

Unguentum Picis Liquidæ, B.P.C.

Oleum Rusci (Oleum Betulæ Albæ).

Birch tar oil is similar in action and uses to oil of cade.

Insecticides

D.D.T. (**dichloro-diphenyl-trichlorethane**).

This is one of the most important members of this group of substances and is lethal to lice, mosquitoes, bed-bugs, etc. It is particularly effective against larval forms, the adult insects being killed much more slowly, depending upon the dose of the drug, the duration of contact, and resistance of the insect. It is a colourless, crystalline solid and is a stable compound, unaffected by sunlight or when dispersed as droplets or as a mist. As the compound does not vaporise, direct contact with the insect is essential. Dilute dispersions in the open are non-toxic to man and the larger animals. It can be applied as a powder (5 to 10% diluted with a suitable inert substance), as an aqueous dispersion, as a kerosene solution or as an oily emulsion. In the control of body lice, underwear can be impregnated with the compound, and as this is insoluble in water it will resist laundering. An emulsion is effective for *pediculosis capitis*, the effect persisting sufficiently long to kill any larvæ which may hatch out from the drug-resistant nits. Sprays should not contain more than 5% of the compound, higher concentrations requiring the use of a respirator. Toxic effects, whilst rare if proper precautions are taken, have been reported from using 2% of D.D.T. in wall distemper in a confined space or warm, damp atmosphere. Symptoms are lassitude, smarting of the eyes, joint pains, irritability and impaired concentration, yellow vision, impaired hearing, anæsthesia, anæmia from red cell destruction and leucopenia. Oily solutions and emulsions, but not the powder, are capable of penetrating the skin. Animals may show diarrhœa, tremors and paresis, and even die from severe toxic changes in the liver, kidneys and heart. The substance has proved fatal in a child when swallowed in kerosene solution. The drug is stored in the body fats. **T.D.E.** (tetrachloro-diphenyl-ethane) is a related compound, and is said to be more lethal to insects.

Gammexane (γ isomer of benzene hexachloride).

This important insecticide is said to be effective against an even wider range of insects than D.D.T. It can be used as a powder or volatilised from a hot plate. It can also be employed as a spray in solution. It forms an emulsion with water or it can be dissolved in kerosene.

Dimethylphthalate (D.M.P.).

This compound is an efficient repellent of mosquitoes, fleas, and the vector of sand-fly fever, giving good protection for one month when applied to the openings in clothing. It is an oily liquid, colourless and odourless, and not irritant to the skin. It must not be applied to eyelids, lips or scrotum. **Dibutylphthalate** is a closely allied substance employed similarly.

p-Dichlorobenzene.

This is a volatile crystalline solid widely used to destroy moths and their larvæ in clothes.

Lethane 384* (β butoxy-β thiocyanodiethyl ether).

This is an effective compound against head lice, but inferior to D.D.T. as it is not so persistent, so that some of the larvæ may hatch out and escape its action. It has an unpleasant odour.

Lysol and Phenol.

Lysol and phenol are the most effective compounds against nits and are superior in this respect to D.D.T. and lethane. **Lauryl thiocyanate** (*Loricide**) as a 25% solution in oil is an effective agent against *pediculosis capitis*. **Sassafras oil,** often used for *pediculosis capitis*, is inferior to these other substances. **Citronella oil** is often employed as an insect repellent. **Pyrethrum** is prepared from a species of chrysanthemum and is a useful insecticide and insect repellent. The active principles are pyrethrins. It can be used as a spray (aerosol), *e.g.* of a mixture in kerosene, or a powder can be employed. An ointment is effective in scabies. **Derris,** an important agricultural insecticide, contains an active crystalline substance, **rotenone,** a 1–2% lotion of which has been used in scabies.

ANTIPYRETICS AND AROMATIC ANALGESICS

ANTIPYRETICS (or febrifuges) are substances employed to reduce the temperature of the body in pyrexia. They may act by reduction of heat formation, or by increasing the loss of heat. The former effect can be brought about by an antiseptic action on the causal organism, by a specific antitoxin or by a low calorie diet and rest. Loss of heat may be effected by increased radiation following dilatation of the skin vessels, or by conduction and evaporation such as result from cold baths or tepid sponging, or from the evaporation of sweat. Since the optimum temperature for the proliferation of pathogenic bacteria is around that of the body, and many of these organisms are susceptible to a rise of even a few degrees Fahrenheit, it follows that fever may be regarded as a protective device to limit infective processes. Provided, therefore, that the patient can maintain strength, it may be undesirable to reduce temperature by the use of febrifuge drugs unless, of course, the drug employed exerts a direct inhibitory action on the invading organism. The temperature of the body is maintained by the heat-regulating centre in the hypothalamus. This centre may be likened to a thermostat which has been set at about 98·4° F., and it controls heat loss by acting upon the medullary centres responsible for vasodilatation (or vasoconstriction) and sweat. In pyrexia the centre has become desensitised, usually by bacterial toxins, and it fails to function at the normal temperature: the "setting" of the thermostat is raised. The specific antipyretics, such as phenazone, act directly upon the centre, resensitising it and thus giving rise to skin vasodilatation and profuse perspiration. These effects do not follow the use of phenazone when the temperature is normal, and this is one proof of the specific action of these drugs. Further proof resides in the fact that if a solution of phenazone *is injected into the hypothalamic region*, a very small dose will produce marked vasodilatation.

Specific Antipyretics
(or **Aromatic Analgesics**)

The action of these substances in fever is discussed above. In addition they exert an important analgesic action on certain types of pain, especially that of a myalgic or neuralgic character. They have much less influence on severe pain of traumatic origin, or that resulting from colic or from acute inflammation. It is suggested that the analgesic action is due to a depression of the conductivity of the synapses in the basal ganglia, in contrast to morphine, which is thought to depress the cortical pain centre.

Various combinations of these drugs, generally aspirin with phenacetin, are widely used in tablet form for the relief of headaches, rheumatic pains, dysmenorrhœa, etc. Direct measurements on the relief of pain in the human subject have shown conclusively, however, that such combinations have no especial merit over the component drugs administered alone. Furthermore the practice of taking several of the standard 5-gr. tablets for a dose has no logical basis. A single 5-gr. dose of aspirin, for example, exerts an analgesic effect lasting 3 to 4 hours; increased dosage merely increases the rate of excretion with no improvement in the degree of analgesia produced. Members of this group are all derivatives of phenol, and they are liable to give rise to various toxic symptoms which are discussed under the individual drugs.

Acetanilidum, 2–5 gr. (*Antifebrin**).

Acetanilide is a powerful antipyretic, and it has been employed as an analgesic in migraine, dysmenorrhœa, sciatica, etc., usually in conjunction with sodium bicarbonate, which reduces its toxicity. Nevertheless idiosyncrasy to the drug is not uncommon, and the toxic sequelæ, including methæmoglobinæmia with cyanosis, are so dangerous that acetanilide is not now greatly used.

Acidum Acetylsalicylicum (Aspirin, *Aspro,* Empirin,** etc.), 5–15 gr.

Aspirin is partly hydrolysed in the tract, but for the most part it is absorbed as sodium acetylsalicylate. The drug exerts the general properties of the salicylates (*q.v.*), but the acetyl group confers upon it much more marked analgesic properties, especially against myalgias. It is, therefore, widely used both as an antipyretic and to relieve the limb pains in influenza and rheumatism. It is a useful, and in reasonable dosage generally harmless, remedy against headache and for the minor "aches and pains," but there is no evidence for the popular belief that aspirin possesses sedative or hypnotic properties. Intolerance to aspirin, although not unknown, is very uncommon, but a few cases of urticaria, localised œdema and asthma following its use have been reported. In fine powder it is used as an insufflation to septic tonsils, its antiseptic action being increased by the slow liberation of salicylic acid *in situ* by hydrolysis. In doses of 60–90 gr. daily with sodium bicarbonate it is used in the treatment of gout because it increases the excretion of urates, and is less toxic than cinchophen (see below).

The following compound powder is used as a mouthwash and gargle in infective conditions:

℞ Pulv. Acid. Acetylsal. .. ℥iſs
Magnes. Peroxid. .. .. ℥ſs
m. fiat pulv.

A level teaspoonful to be stirred into half a tumbler of warm water for use.

Calcii Acetylsalicylas, 5–15 gr.

The calcium salt of acetylsalicylic acid is sometimes better tolerated and more effective than aspirin. It may be preferable to aspirin for administration to children.

Amidopyrina (*Pyramidon**), 5–10 gr.

The action of amidopyrine is similar to that of acetanilide, but the analgesic effect lasts longer. In common with the other members of the group (with the exception of aspirin) it exerts some toxic action on the myocardium, also it may give rise to methæmoglobinæmia. It has been much used against dysmenorrhœa, but the possibility of agranulocytosis following its use necessitates caution in prescribing, especially as it is not uncommon for irresponsible patients grossly to exceed the dosage ordered in the hope of obtaining speedier relief from pain.

Tabellæ Barbitoni et Amidopyrinæ, B.P.C. (*Veramon**). Dose: 1 tablet.

Phenacetinum, 5–10 gr.

Apart from aspirin, phenacetin is the least toxic of this group of analgesic antipyretics and it is usually well tolerated. Its mode of action is precisely similar to that of amidopyrine, etc. Phenacetin is insoluble in water and is usually employed in tablet form.

Tabellæ Codeinæ Compositæ, N.F. (*Veganin,** sim.).

This compound tablet, which is widely used as an analgesic, contains four grains each of aspirin and phenacetin with ⅛ gr. of codeine phosphate. The proportion of codeine present is too small to have any action on pain in general, but when the tablet is administered in cases of spastic dysmenorrhœa the uterine spasm may be relieved by the direct action of codeine on the muscle fibre.

Phenazonum (Antipyrine), 5–10 gr.

Phenazone is freely soluble in water. Its action is similar to that of amidopyrine but it is much less seriously toxic; nevertheless it is more liable to cause skin eruptions.

Phenazonum cum Caffeina Effervescens, B.P.C., 1–2 dr.

This granular effervescent preparation is stirred into half a tumbler of water and used to relieve migraine and other types of headache.

Novalgin,* 5–15 gr.

Novalgin is a proprietary derivative of phenazone which exerts a similar action to the latter drug but is stated to be less toxic. It is administered orally or, as a 50% solution, parenterally, and is particularly effective against myalgias and articular rheumatism. In Continental practice, the injection is claimed to be successful for the relief of biliary colic and other severe types of pain when given intravenously.

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Other important analgesics which are not members of this group are the **opium alkaloids,** diamorphine and pethidine. These are considered in the section on Narcotics. Miadone is considered below.

Miadone (*Amidone, Physeptone**).

This is a recently introduced synthetic compound which is claimed to be a potent analgesic. It has few side reactions and does not induce drowsiness, apathy or respiratory depression. Some degree of tolerance may be established. Euphoria, dizziness, blurred vision, nausea and vomiting may occur, and addiction cannot be ruled out. Tablets of 5 mg. for oral use and ampoules of 10 mg. for parenteral administration are available. The dose is 5–30 mg., depending upon the severity of the pain. Chemically it is dl-2-dimethylamino-4 : 4 diphenyl-heptane-5-one hydrochloride. Miadone appears to have a suppressive action on a useless cough similar to that of codeine.

Drugs acting in Gout

Cinchophenum, Off. (*Atophan**), 5–15 gr.

Cinchophen is a derivative of a quinoline carboxylic acid. When given by mouth it increases considerably the excretion of urates in the urine. With patients on a purine-free diet the same effect occurs, and in such cases obviously the urates must be derived from the tissues under the influence of the drug. In general, the blood urate level falls, but in some cases the level rises, and this fact lends further credence to the view that cinchophenum stimulates the formation of urates. It is thought that the increased excretion is due to a lowering of the renal threshold for urates.

Cinchophen, like the salicylates, is an antipyretic and analgesic, and it is used in gout mainly to relieve the pain and to aid in the elimination of urates. It is possible, too, that it may assist the absorption of urates from joints and tophi. The chief use of the drug is for the prevention of exacerbations of the disease and for chronic gout. It is not suitable for the treatment of the acute attacks. The drug has been used in rheumatism and fibrositis, but the risk of toxic manifestations does not warrant its administration for these conditions. Toxic effects which may arise from cinchophen therapy are skin eruptions, anaphylactoid symptoms, dyspepsia and a toxic hepatitis which may proceed to acute yellow atrophy, especially if there is pre-existing impairment of the liver. To minimise danger it is usual to administer the drug for three successive days each week, followed by an interval for four days, abruptly discontinuing its use if any toxic symptoms develop. A small preliminary dose should be given to test for idiosyncrasy to the drug.

Neocinchophenum (*Tolysin**), 10–15 gr.

This drug is related chemically to cinchophen and is prescribed for the same purposes. It is less toxic than cinchophen, but the same care in administration is needed.

Colchicum (Corm and seeds).

Colchicum owes its activity to the alkaloid colchicine. It relieves the pain of gout and reduces the inflammation of the acute attack, but it effects no increase in the amount of urate excreted, and is of no value between attacks and in chronic gout. Colchicum is irritant to the mucosa of the tract and may produce vomiting and purgation. The drug is usually given in maximal dosage every four hours until improvement occurs or there is nausea or diarrhœa. Treatment is often combined with magnesium carbonate.

Colchicina, $\frac{1}{120}$–$\frac{1}{30}$ gr.

Crystalline colchicine 0·5 mg. hourly for a total of 4–8 mg. may prove effective in acute gout. The local application of an oily solution has been used against *condylomata acuminta.*

Tinctura Colchici, Off., 5–15 min.

For details of the use of **sodium salicylate** and **aspirin** in gout (*q.v.*).

Diaphoretics

Diaphoretics (or sudorifics) are substances which cause increased perspiration. They usually dilate the skin vessels, hence loss of heat occurs by radiation and by evaporation of sweat. Of especial importance, however, is the fact that bacterial toxins are excreted with the sweat. Saline diaphoretics cause hydræmia with consequent increased activity of the sweat glands and the kidneys. The common saline diaphoretics are:

Liquor Ammonii Acetatis Fortis, Off. 15–60 min.
Potassii Acetas, 15–60, gr.
Potassii Citras, 15–60 gr.
Sodii Salicylas, 10–30 gr.

Other diaphoretic or antipyretic substances apart from those described in this chapter include:

Alcohol, Antiseptics and Chemotherapeutic Agents (Quinine, etc.), Dover's Powder, Ipecacuanha, Pilocarpine, Potassium Antimonyl Tartrate, Spirit of Nitrous Ether.

The pharmacology of these substances is discussed elsewhere in this volume.

HYPNOTICS AND NARCOTICS

Although some writers use the terms *hypnotic* and *narcotic* interchangeably, it is legitimate and useful to regard the drugs comprised within these headings as falling into two well-defined groups. In the classification here adopted, the term hypnotic is applied to drugs whose characteristic effect is sedation of the central nervous system and, in sufficient dosage, quiet sleep. In addition to sleep, narcosis involves relief or diminution of pain by central action, and all narcotics tend to give rise, also, to a phase of euphoria or excitement prior to the induction of sleep. These and other differences to be discussed, may be explained by considering the possible site of action, within the cerebral hemispheres, of the drugs concerned.

In the case of the hypnotics the initial effect is to produce depression at the thalamic sleep level, following which there is a slight ascending and a more pronounced descending depression of cerebral activity. The latter involves the motoric centres, the hypothalamus and the medulla, which are strongly affected. Except in anæsthetic dosages (*e.g.* basal narcosis, *q.v.*), the hypnotics do not extend high enough into the sensory cortex to affect the pain centre, and **sleeplessness due to pain cannot be controlled by the exhibition of simple hypnotics.** In contrast with the foregoing, narcotic drugs produce a descending depression of the sensory cortex which commences with the highest centres and proceeds in conformity with the "Law of Dissolution"—the mental faculties being lost in the reverse order to which they are acquired. This process is well illustrated by the objectionable manifestations of alcoholic intoxication. This depression involves, of course, the pain centre, and all narcotics give rise to some degree of analgesia of central orign. In therapeutic dosage, narcotics do not depress the motor cortex; indeed the volatile members of the group may give rise to considerable motoric irritation. Finally, the narcotics are pre-eminently drugs of addiction, because when the phase of euphoria wears off there is left behind a trough of psychical depression with a lowered anxiety threshold which, of itself, provides a temptation to fresh indulgence.

The classification, suggested above, applies to the following drugs:

Hypnotics	**Narcotics**
Barbitone, and related drugs.	Alcohol.
Carbromal.	Amylene hydrate.
Chloral hydrate.	Diamorphine.
Sulphonal.	Ether and Chloroform (in the first stage of anæsthesia).
Urethane.	Morphine.
	Paraldehyde.

The more or less selective action of many of the above-mentioned drugs, including the general anæsthetics, on the central nervous system, is associated with their greater solubility in lipoids than in water (aliphatic hypnotics and narcotics). Narcosis is accompanied by dehydration of the nerve cells and a decrease in their permeability. It is suggested that this is due to their dissolving in the lipoids of the cell membrane, as a result of which there is a redistribution of these lipoids. Those at the surface, termed surface active lipoids, are displaced to the interior of the membrane and replaced by less hydrophylic lipoids, with a rise in surface energy, dehydration of the cell and diminished permeability. The surface lipoids thus displaced to the interior may be enzymes concerned in oxidation processes, and their removal from the surface may be followed by diminished oxidation. Decreased permeability may result in reduced transportation of carbohydrates with further reduction in metabolism. Another suggestion is that a state of electrical negativity is induced at the cell surface by the narcotic, which prevents transmission of the normal impulse.

Alcohol (Ethyl Alcohol, Ethanol).

Alcohol taken by mouth causes a reflex stimulation of the salivary and peptic glands; by irritating the mucosa it is a reflex stimulant in fainting. It is absorbed from the stomach and small intestine, and exercises a depressant action on the central nervous system. The higher centres are first affected, with impairment of the sense of proportion, judgment and self-criticism, and, in the early stages of alcoholic poisoning, euphoria is common. At no stage is alcohol a stimulant to the mental faculties. Apparent stimulation, which may occur, is due entirely to the suppression of inhibitions, and there is a wealth of pharmacological wisdom in the aphorism *in vino veritas*; the primitive being revealed when alcohol has removed restraint. Alcohol causes dilatation of the skin vessels and diaphoresis by its depressant action on the vasomotor centre, and also by its metabolism and consequent heat production in the tissues. Loss of heat by radiation, etc., is, however, relatively large, and if the drug be employed as a restorative in physical exhaustion it is supremely necessary to wrap the patient warmly. In general, the habit-forming properties of this drug are sufficient to discredit its clinical use except, perhaps, for the psychological effect in the terminal stages of neoplasm, etc. Taken in conjunction with ordinary diet, alcohol replaces the normal fuels which are liable to be deposited as fat, causing obesity. Fatty degeneration of the liver, etc., is a result of addiction; other sequelæ are chronic gastritis, and sometimes cirrhosis of the liver. There is also defective absorption both of vitamin A and of the B-complex, possibly as a result of chronic gastritis and enteritis. This vitamin A deficiency is associated with conjunctivitis and inflammation of mucous membranes found in alcoholics. Peripheral neuritis and chronic mental degeneration ("softening of the brain") result from deficiency of vitamin B, and even *delirium tremens* will respond to large doses of this vitamin.[1] *Acne rosacea* is frequently associated with alcoholic gastritis. Following ingestion of the drug an average blood content of 0·1% produces the early effect of alcohol, 0·2% generally produces disorders of conduct, while 0·3%–0·5% means stupor; these figures are approximately true in all cases. Apart from the quantity taken, the proportion in the blood is controlled by the factors of rate of absorption from the alimentary tract, body-weight, the rate of metabolism, and possibly a selective discharge into the bloodstream by the liver. By irritating the renal tubules alcohol acts as a diuretic. Externally, alcohol (10%–15%) is used as an evaporating lotion; 70% alcohol is used to sterilise skin areas, while 95% alcohol hardens the skin and is used to prevent bed-sores. Alcohol is largely used as a solvent and preservative in the manufacture of medicinal preparations. Potable alcoholic liquors, such as whisky, brandy and champagne, are used for sedation, and to improve the appetite and maintain strength in fevers, etc. Possibly as a psychological effect, brandy, by mouth, may relieve *angina pectoris* in the absence of nitrites. Alcohol (80% to 100%) is injected into the Gasserian ganglion for the relief of intractable trigeminal neuralgia, into other nerves for the relief of severe and persistent neuritis, and into the upper dorsal roots for *angina pectoris*.

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[1] It is now considered that choline deficiency is an important factor in the genesis of alcoholic fatty infiltration and portal cirrhosis of the liver.

By mouth, 50 mls. of a 7% solution is commonly employed as a stimulant of gastric secretion in the fractional test meal.

Spiritus Methylatus Industrialis, Off.

Contains 5% of methyl alcohol in ethyl alcohol 95%, and is used as a solvent for external preparations.

Spiritus Rectificatus, Off. (Spiritus Vini Rectificatus).

Contains 90% of ethyl alcohol.

Amyleni Hydras, ½–1 fl. dr.

Amylene hydrate possesses narcotic properties resembling those of paraldehyde. It is more depressant to the heart than the latter, but is stated to be safer in that regard than chloral hydrate. Small doses may produce excitement. The drug is partially eliminated by the lungs. The following is a suitable draught:

℞	Amylen. Hydrat.	..	..	ʒi
	Tinct. Card. Co.	..	..	ʒss
	Syr. Zingib.	..	..	♏xx
	Aquam Cinnam.	..	..	ad ℥i
	ft. haust.	℥ss–℥i pro dos.		

Amylene hydrate is used as a solvent in bromethol (*q.v.*).

The Barbiturates

Barbitonum, 5–10 gr. (Barbitalum, *Veronal**).

Barbitone is a pure hypnotic; it produces deep, refreshing sleep within some 30 minutes of ingestion and, except when habitually taken, there are generally no after-effects. Idiosyncrasy is not unknown, however, and vertigo and skin eruptions may follow small dosage, larger doses may cause collapse by circulatory and respiratory depression. Barbiturates, in general, tend to bring about a state of weakness, amnesia and mental confusion in the addict, and if the patient has access to further supplies he may take repeated doses, forgetting about previous ones, until syncope supervenes. The barbiturates are liable to become drugs of addiction, and elimination being slow, cumulation occurs with habitual use and may give rise to diplopia, vertigo and even moral degeneration. In cases of acute poisoning, prolonged coma is typical, with death following respiratory depression or hypostatic pneumonia. Treatment should be on the lines of an intramuscular camphor depot or intravenous nikethamide and injections of strychnine hydrochloride and the inhalation of oxygen with carbon dioxide mixture. A modern practice is to administer picrotoxin intramuscularly, or preferably intravenously, either 5–10 mg. at intervals of 20–30 minutes, depending on the response of the patient, or as a 1 : 1,000 solution, giving 1 mg. per minute until the pupillary and corneal reflexes return. Should mild convulsions be produced, these can be controlled immediately by the intravenous injection of any soluble barbiturate, such as hexobarbitone sodium. (For use of amphetamine, *q.v.*) Barbitone is slowly eliminated in the urine, and habitual use is liable to give rise to pathological changes in the kidney. The drug is a useful hypnotic in nervous insomnia, the delirium of fevers, etc., and it is sometimes used to check vomiting of cerebral origin, and as a sedative in hysterical conditions.

Tabella Barbitoni et Amidopyrinæ, B.P.C. Dose: 1 tablet.

This combination of a hypnotic and an analgesic is useful in the control of sleeplessness due to pain. Prolonged use may give rise to agranulocytosis owing to the presence of amidopyrine.

Barbitonum Sodium, 5–10 gr. (*Medinal**).

This soluble sodium derivative of barbitone is used in solution, rectally, by hypodermic injection, or, in tablet form, by mouth. Its action is identical with that of barbitone.

Hexobarbitonum, 4–8 gr. (*Evipan**).

Hexobarbitone is a rapidly acting hypnotic possessing a low toxicity. After absorption it is speedily detoxicated and the duration of its action is very brief. Once asleep, however, the patient may continue in a natural sleep after the action of the drug has worn off. Hexobarbitone is a useful drug for the control of sea-sickness, especially for short crossings. Hexobarbitonum Sodium (*q.v.*) is used intravenously as an anæsthetic, and an antidote in cases of strychnine poisoning and other convulsions.

Methylphenobarbitonum, Off. ½–6 gr. (Phemitone, *Prominal**).

Phemitone is a very stable barbiturate which is slowly excreted and exerts a prolonged depressant action on the motoric centres, but only to a small extent on the sensory cortex. It is employed therefore as a maintenance drug in epilepsy and migraine, and as an antispasmodic.

Phenobarbitonum, ½–2 gr. (Phenobarbital, *Luminal**).

The action of phenobarbitone is qualitatively similar to that of barbitone (*q.v*). Its action is, however, much more prolonged, and it is administered in small doses as a sedative in the treatment of epilepsy and vertigo, and to control nervous excitement. Toxic symptoms are largely the same as with barbitone, but it is especially liable to give rise to skin eruptions and occasionally giddiness, inco-ordination, depression and pyrexia.

Tabella Phenobarbitoni et Theobrominæ, B.P.C. 1–2 tablets. (*Theominal,* Theogardinal.**)

This compound is often prescribed to counteract the nervous excitement and insomnia associated with hyperpiesis and angina pectoris. The diuretic effect of theobromine assists in preventing further rise in the blood-pressure.

Phenobarbitonum Sodium (Phenobarbital Solubile, *Luminal-Sodium**).

The soluble sodium derivative of phenobarbitone is occasionally given hypodermically. Solutions should be freshly prepared, since the drug is unstable when dissolved in water. The increasing habit of adding phenobarbitone sodium to multiple-dose mixtures is an indication that many prescribers are unaware of the instability of the drug in solution.

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A great number of derivatives of barbituric acid are available commercially for use in insomnia, nervous excitement and delirium.

Allobarbitonum, B.P.C. (*Dial**), ½–3 gr.

This compound is more readily absorbed than barbitone. Idiosyncrasy with rash and fever may occur.

*Allonal.**

This is allylisopropylbarbiturate of amidopyrine combined with amidopyrine, and is therefore an analgesic as well as hypnotic. Dose 1–4 tablets.

Butobarbitonum (*Soneryl**), 1½–3 gr.

This is much more active and more toxic than barbitonum and is a commonly-used hypnotic. It can also be given rectally. The sodium salt given in capsules in doses of 0·15 gm. can be employed as a basal hypnotic in obstetrics and anæsthesia.

*Amylobarbitone** (5-isoamyl-5 ethylbarbituric acid).

This compound is a useful sedative and hypnotic, with an action of short duration and few after-effects. It is used orally in doses of ·1–·3 gm. in the treatment of insomnia and excitement. The soluble sodium salt can be used orally in doses up to ·6 gm., and a 10% solution can be given intravenously in doses of 0·3–1 gm. in the treatment of convulsions of tetanus and strychnine.

*Amytal** (isoamylethyl barbituric acid).

This is used in doses of up to 1 gr. as a sedative, of 1½–5 gr. as a hypnotic, and of 3–10 gr. as a basal narcotic and to control convulsions. The sodium salt can be given in similar doses by mouth or rectally, whilst 10% solutions can be injected parenterally as a basal narcotic or as an anti-convulsant. Great care must, however, be exercised as a marked fall in blood-pressure may occur with intravenous injection, and if given intramuscularly not more than 5 ml. should be injected at any one point.

Pentobarbitonum Sodium, Off. (*Nembutal**), 1½–3 gr. (see p. 195).

*Phanodorm** (Cyclobarbitone), 1½–6 gr.

This drug has a more rapid action than barbitone and is more rapidly eliminated. A similar compound is *Sodium Hebaral.**

*Pernocton.**

This is given intravenously in doses of 4½ gr. (in 3 ml.). It has a similar action to sodium amytal, but is more powerfully hypnotic and does not cause a fall in blood-pressure. Similar oral preparations are *Seconal** (1½–3 gr.) and *Sandoptal** (3–6 gr.).

*Somnifaine.**

This consists of the diethylamine salts of barbitone and allylisopropylbarbituric acid dissolved in a glycerine-alcoholic solution. It is used orally as a hypnotic in doses of 20–60 drops. It is given intramuscularly (or intravenously in urgent cases) to control mania, delirium or convulsions, the dose employed being 2–4 ml.

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Bromides.

The specific action of the bromide ion is to increase the resistance of the synapses of the reflex conducting paths, especially of the brain and medulla, but only slightly of the cord. This insulation from afferent stimuli permits mental composure, while direct depression of the motoric centres further aids an hypnotic effect.

Bromides are administered in all forms of nervous excitability and in the treatment of epilepsy. Prolonged administration leads to progressive replacement of the tissue chloride by bromide, and there follow psychical depression, ataxia, mental confusion, impotence, etc. At or above a blood level of 250 mg. per cent. of bromide, delirium, hallucinosis, and even a paranoid state have been reported. Anæsthesia of the palate is an early indication of overdosage. Papular or acneiform rashes may follow the use of bromide; these are said to be checked by the concurrent administration of arsenic. The treatment of bromide intoxication is to give sodium chloride 10–15 gm. daily by mouth or, in severe cases, intravenously. The principal inorganic bromides in use are:

Ammonii Bromidum, 5–30 gr.

Potassii Bromidum, 5–30 gr.

Sodii Bromidum, 5–30 gr.

Calcium bromide and calcium brom-lactobionate (*Calcibronat**) are alternative preparations to the above.

*   *   *   *   *   *

Carbromalum, 5–15 gr. (*Adalin**).

Carbromal is a brominated open-chain ureide not chemically related to the barbiturates. It is a safe sedative and mild hypnotic, especially useful in pædiatrics. Being very insoluble, it is best administered as a powder followed by a hot drink. Its depressant action is due to the molecule as a whole, no bromide ions are liberated and carbromal is useful, therefore, to replace treatment by the inorganic bromides when these give rise to "bromism."

Bromoisovalerianylurea (*Bromural*,* *Dormigene**), 5–10 gr.

This is given orally as a sedative and hypnotic. It acts within ½ hour and its effect lasts for about 4 hours, and is often followed by natural sleep. The drug, given in doses of 5 gr., two or three times daily before travelling, is a useful sedative in the prevention of sea-sickness.

Sedormid* (allylisopropylacetylurea).

This substance, like carbromalum, is an open-chain ureide As a sedative it is given in doses of 2–4 gr. three times daily, and as a hypnotic in doses of 8 gr. Thrombocytopenic purpura has followed its use.

Chloralis Hydras, 5–30 gr.

Chloral hydrate occurs as translucent crystals possessing a characteristic smell. It is a rapidly acting sedative and hypnotic, and is used in nervous insomnia and, often with bromides, to relieve the disturbed rest of teething infants and to control convulsions. In small doses the drug is a useful sedative in nervous excitement, but the danger of fostering an addiction must be remembered. Hypnotic doses depress the vasomotor centre, dilating the skin vessels and causing a fall in blood-pressure. Sleep occurs about half an hour after the dose is taken and lasts some six hours. Owing to rapid detoxication and elimination, it leaves no drowsiness or headache the next morning. When, however, chloral hydrate is combined with a bromide, "carry-over" symptoms may be noticed. Large doses produce coma, with absent reflexes, and, finally, may paralyse the respiratory centre. The myocardium is directly depressed, and its degeneration, together with fatty degeneration of the liver, can be produced by continued large doses to experimental animals. There is no evidence, however, that these results are to be anticipated from normal therapeutic dosage, and most clinicians employ chloral hydrate as a sedative in heart disease. The drug is excreted in the urine conjugated with glucuronic acid (forming urochloralic acid) and is non-cumulative. Chloral hydrate, unless well diluted, is irritant to the mucosa. To control the convulsions in eclampsia, tetanus and strychnine poisoning, doses of 1 or 2 drachms in 4 fluid ounces of thin mucilage of starch are given per rectum. Applied externally to intact skin, chloral penetrates and depresses the sensory nerve ends, thus producing a local analgesia. As a hypnotic draught:

℞		
℞	Chloral Hydratis	gr. xv
	Sodii Bromid.	gr. xx
	Ext. Glycyrrh. Liq. ..	♏xv
	Aquam Anisi	ad ℥i
	ft. haust.	pro dos.

Chlorbutol, 5–20 gr. (*Chloretone**).

Chlorbutol is a mild sedative and antiseptic. It exerts a local action on the stomach and is given to check sea-sickness and post-operative vomiting. It is used externally to relieve pruritus and, dissolved in liquid paraffin, is applied to the nose and throat in catarrhal conditions.

Hyoscina (*q.v.*).

The Opium Alkaloids

The pharmacology of opium is the resultant of the actions of its alkaloids. These are divided into the phenanthrenes (morphine, codeine, etc.) and the isoquinolines (narcotine, papaverine, etc.). The uses of opium are substantially those of morphine, but because of the action of the quinolines in relaxing smooth muscle, opium, or papaveretum (*v. infra*), is preferred to relieve the pain of biliary, intestinal and renal colic, to check diarrhœa and to promote diaphoresis. Opium (or morphine) is especially dangerous to infants at the breast or during the first twelve months of life, but afterwards tolerance rapidly develops. In old age, however, respiratory embarrassment is common, and opium is then especially dangerous.

Opium Pulveratum, B.P., $\frac{1}{2}$–3 gr. (Opium Granulatum, U.S.P.).

Powdered opium, adjusted to contain 10% of morphine.

Papaveretum, $\frac{1}{12}$–$\frac{1}{3}$ gr. (*Alopon,* Opoidine,* Omnopon,* Pantapon**).

This is an injectable preparation of the total alkaloids of opium adjusted to contain 50% of morphine. It can be used for the same purposes as injections of morphine, and it is preferable not only on account of the antispasmodic action of papaverine and narcotine, but because those alkaloids have, also, a stimulating action on the respiratory centre. For pre-operative sedation it is now customary to employ an injection of papaveretum with hyoscine (scopolamine).

Pulvis Cretæ Aromaticus cum Opio, 10–60 gr., Off.

Used in the treatment of diarrhœa.

Pulvis Ipecacuanhæ et Opii, 5–10 gr. (Dover's Powder), Off.

Used as a diaphoretic and analgesic.

Tinctura Opii, 5–30 min. (Laudanum), Off.

A convenient liquid preparation for oral administration. Thirty minims contain morphine $\frac{1}{3}$ gr. (*Nepenthe** is about $\frac{4}{5}$ as strong as this tincture.)

of antidiuretic pituitary hormone as well as upon the reduced intake of water. Small doses of morphine are used orally to depress the respiratory centre and so reduce a useless cough and relieve dyspnœa. Severe depression of the centre leading to Cheyne-Stokes respiration, and ultimately respiratory failure, follow large doses of the drug, and it should be administered with the greatest discretion in those cases of injury and shock where there is a respiratory embarrassment, and in the later stages of pneumonia where there is much cyanosis. In these cases the use of oxygen greatly reduces the risk with morphine. The effects of morphine on the heart are comparatively slight. By conferring tranquillity on the central nervous system it may reduce a tachycardia of purely nervous origin, but bradycardia is never produced. Beneficial effects of morphine in the relief of cardiac asthma, coronary thrombosis and angina may also be ascribed largely to the central tranquillising effect of the drug. Overdosage or prolonged administration of morphine may sufficiently depress the hypothalamic parasympathetic ganglia to lead to urinary retention by causing atony of the detrusor. A similar effect can be produced by the abuse of hypnotics such as barbitone, and is a not uncommon sequel of general anæsthesia. Like all narcotics, morphine is a drug of addiction, and it is especially dangerous because of the severe physical reactions which accompany its withdrawal. These reactions can be mitigated by the administration of codeine and of amphetamine (*q.v.*). The local application of morphine has no analgesic effect on the sensory nerve ends. To obtain the maximum therapeutic effect it is necessary to inject subcutaneously one of the soluble salts of morphine listed below, and it is not uncommon to combine with the injection a small dose of atropine sulphate to minimise pylorospasm, etc., and as a stimulant to the respiratory centre. The combination is suitable for the relief of intractable pain and for pre-operative sedation, although for the latter purpose papaveretum (*q.v.*) is now preferred. **Morphine poisoning** is characterised by deep coma, Cheyne-Stokes respiration and pin-point pupils. Death finally occurs by paralysis of the respiratory centre. In the terminal stage incipient asphyxia, by causing an outpouring of adrenaline, dilates the pupil. Treatment should involve gastric lavage with dilute potassium permanganate solution to destroy the alkaloid, since by whatever route it is taken some excretion into the stomach takes place. Caffeine sodium benzoate, theophylline with ethylenediamine, or nikethamide should be injected to stimulate the respiratory centre. Oxygen with carbon-dioxide mixture must be used also. It is claimed that the administration of amphetamine reduces the depressive and increases the analgesic action of morphine. Deep intramuscular injection of morphine is preferable in patients with peripheral circulatory failure in whom hypodermic injections may result in poor absorption and failure to relieve pain, so that further doses are given. With restoration of an adequate circulation a toxic amount of the drug may then be absorbed.

Morphinæ Hydrochloridum, ⅛–⅓ gr.
„ **Sulphas,** ⅛–⅓ gr.
„ **Tartras,** ⅛–⅓ gr.

Liquor Morphinæ Hydrochloridi, Off. 5–30 min.
A convenient solution for oral administration.

Tinct. Chloroformi et Morphinæ, B.P.C. (Chlorodyne). Dose: 5–10 min.

Monoacetlymorphine, a recent American preparation, is claimed to be more potent and less toxic than the commonly used preparations.

Suppositorium Morphinæ (¼ gr.), Off.

Æthylmorphine Hydrochloride (*Dionin**). Dose: 1/10–½ gr. orally; 1/24–⅛ gr. by injection.

Used as a sedative for spasmodic cough. Solutions 1–5% employed for the relief of pain in glaucoma, iritis and keratitis. Syrup Cocillana Co. (*Cosylan**) is a sedative expectorant containing ethylmorphine. Dihydromorphine (*Dilaudid**) has a similar action to morphine, but is more powerful and toxic, and is effective in smaller doses (½ gr. orally, 1/32 gr. subcutaneously). Vomiting and constipation are said to be less frequent.

Narcotina, 1–3 gr.

Narcotine is one of the isoquinoline alkaloids present in opium. It first mildly depresses the cerebral centres, then strongly stimulates the cord; for these reasons it has aphrodisiac qualities. Like papaverine (*q.v.*) it stimulates the respiratory centre and also relieves spasm of all involuntary muscle. It is effective by mouth and is stated to potentiate the analgesic effect of morphine.

Cotarninæ Chloridum, ⅓–1½ gr. (*Stypticin**).

Cotarnine is obtained by the oxidation of narcotine. It causes uterine contraction and is used to control uterine hæmorrhage locally, as a 2% solution on a tampon, or by hypodermic or oral administration.

Pethidine, 25–100 mg.

Pethidine is the ethyl ester of 1-methyl-4-phenylpiperidine 4-carboxylic acid and the salt used is the hydrochloride. It is similar in chemical structure and pharmacological action to atropine and morphine, but is less depressant to the respiratory centre than the latter, and not so effective in relieving severe pain. It has analgesic, sedative and antispasmodic actions. The drug appears to be generally more effective for the relief of visceral pain than of skeletal and neurological pain, and it is particularly valuable for the relief of colic. It is used in the relief of renal, biliary and intestinal colic, dysmenorrhœa and labour pains, angina pectoris, post-operative pains and, in fact, in any condition in which pain does not respond to the aromatic analgesics. In obstetrics it is used in combination with barbiturates. A hypnotic effect is produced in 10 minutes. Pethidine, when used orally, appears to have a considerable margin of safety, with toxic symptoms unusual and not serious, provided that the daily dosage does not exceed 250–500 mg. Tolerance may develop, and serious symptoms of addiction have resulted from long continued doses, generally 1,000 to 2,000 mg. daily, particularly when given parenterally, and to psychopathic patients. Intoxication results in euphoria, drowsiness, vertigo, faintness, impaired memory, sweating, vomiting, pyrexia, anæsthesia, mydriasis, disturbances of micturition, failure of libido, confusional psychoses, emaciation, convulsions and occasionally death from respiratory failure. Withdrawal symptoms are mild and consist of restlessness, insomnia and malaise. They can be controlled by insulin.

β-Pethidine is ethyl 3-phenyl 1-methyl-piperidine 3-carboxylate.

This is used in similar doses to the above, either orally or by injection. It is slower and less powerful in its action than pethidine, inducing sleep in about ½ hour when injected hypodermically. It has even less toxicity than pethidine, nor does it induce euphoria.

Paraldehydum, ½–2 fl. dr.

Paraldehyde, a liquid with nauseous smell and taste, is a rapidly acting narcotic, but has little or no depressant action on the heart or medulla. It produces intoxication similar in character to that of alcohol, but the various stages of intoxication succeed each other in such rapid sequence that it is usually difficult to identify their passage. If the dosage be too small, however, excitement may occur without sleep. Full narcotic doses are used in cardiac and mental diseases. Addiction may occur, but the fact that the drug is partly eliminated by the lungs, and can be smelt in the breath for 48–96 hours after its ingestion, is a strong safeguard against its abuse. As a draught the following disguises fairly well the unpleasant taste and minimises gastric irritation:

℞	Paraldehydi	ʒij
	Ext. Glycyrrh. Liq.	ʒſs
	Mucilaginis Acaciæ	ʒij
	Syrup. Aurantii	ʒſs
	Aquam Anisi	ad ℥i

ft. haust. pro dos.
To be taken in a wineglassful of water.

As a narcotic, paraldehyde possesses the disadvantage of promoting diuresis by irritation of the renal tubules and of the bladder. For basal anæsthesia the drug is used *per rectum* in the proportion of 1 fl. dr. per 14 lb. body-weight, with a maximum dose of 1 fl. oz. The following is a suitable preparation for the purpose, to minimise rectal irritation:

℞	Paraldehydi	℥i
	Olei Arachis	℥i
	Pulv. Acaciæ	℥ss
	Aquam	ad ℥vi

ft. emulsio.

The quantity *of the emulsion* to be used is 6 fl. dr. per 14 lb. body-weight, with a maximum of 6 fl. oz. The diuretic effect above-mentioned is, however, a disadvantage. Paraldehyde can be injected intravenously or intramuscularly to control convulsions, *e.g.* in eclampsia.

Phenytoinum Sodium, Off. 1½–3 gr. (*Epanutin**).

Phenytoin Sodium is sodium diphenylhydantoinate, a powerful anticonvulsant with little hypnotic action. On this account it is a more suitable drug than the barbiturates for the control of epilepsy but it is liable to give rise to a number of toxic reactions, and its use demands great caution. Nausea, vertigo and rashes may occur, and in some cases purpura or exfoliative dermatitis. It should not be administered to young children or to debilitated patients.

Triodone* (3, 5, 5-trimethyloxazolidine-2-4-dione).

This anticonvulsant drug is used in the treatment of *petit mal*, myoclonic and akinetic epilepsy. Each capsule of the drug contains 0·3 gm., and the daily dose is 1–2 gm. Toxic effects include drowsiness, rash, nausea, and a "glare effect" when looking at moderately bright objects. It may give rise to leucopenia and even agranulocytosis.

Sulphonal, 5–20 gr.

Sulphonal is a slow-acting hypnotic which is excreted slowly and causes drowsiness for many hours. It is used occasionally in mania to depress the motor areas of the brain, and sometimes to relieve mental distress; but administration should be for short periods only, and free evacuation encouraged. Prolonged administration results in cumulation with liver damage, destruction of the red cells and hæmotoporphyrinuria.

Urethanum (Ethyl Carbamate), ¼–½ dr.

Urethane is a very mild and safe hypnotic; it has no depressant action on the heart and is especially valuable for children. It is excreted as urea, and exerts, therefore, some diuretic action. Urethane has recently been used in the treatment of leukæmia in doses of 3–10 gm. daily. Temporary improvement, particularly in the myeloid type, has been claimed. Nausea and vomiting may occur.

Valeriana (a root).

This drug contains esters of valeric acid which act as carminatives, antispasmodics, and possibly as sedatives to the central nervous system; the mechanism of the last action being obscure. Preparations of valerian are used in nervous dyspepsia, and generally to assist in the relief of anxiety states.

The following is a useful valerian mixture for flatus associated with nervous irritability:

℞	Sodii Bicarb.	gr. xv
	Ammon. Bromid.	gr. v
	Tinct. Valer. Ammon.	♏xv
	Tinct. Rhei Co.	♏x
	Syrup Zingiberis	ʒss
	Spirit. Chlorof.	♏v
	Aq. Menth. Pip.	ad ℥i
	ft. mist.	pro dos.

Tinctura Valerianæ Ammoniata, ½–1 fl. dr., Off.

ANÆSTHETICS

ANÆSTHETICS are substances employed to produce a controlled general unconsciousness (general anæsthesia) or anæsthesia of a localised area (local anæsthesia), generally with a view to the painless performance of a surgical operation. The mode of action of general anæsthetics has been already discussed in the chapter on Hypnotics and Narcotics. General anæsthetics can be administered by inhalation, intravenously or rectally; the methods of local anæsthesia will be considered later. Defined on a fundamental basis the purpose of anæsthesia is to render the subject as suitable as possible for the surgeon. This involves abolishing pain and psychic trauma and the immobilisation of the patient. At the same time the vital physiological processes must be maintained, and post-operative healing facilitated by preventing restlessness and insomnia by suitable methods of sedation. The effects produced by general anæsthetics occur in fairly well-differentiated stages which, however, vary in intensity and duration with the various anæsthetics employed. The following are the stages:

Stage I: Analgesia. This is well seen with nitrous oxide and with trichlorethylene. It is of short duration with ether.

Stage II: Excitement. Then follow confusion, restlessness, a feeling of asphyxia, vertigo, dilatation of the pupils, irregular respiration, and finally unconsciousness. This stage is not always well marked.

Stages I and II constitute the phase of **Induction.**

Stage III: Surgical Anæsthesia. This is indicated by muscular relaxation, loss of sphincter control, corneal anæsthesia, and slowing of the heart rate if tachycardia develops in Stage II.

Stage III is usually divided into *four phases*; as anæsthesia deepens from the first to the fourth phase so the respiration becomes automatic and shallow, while the pupils, which are often small at first, dilate and do not react to light.

Stage IV: Medullary depression and, later, paralysis of the bulbar centres may occur. There is a marked fall in blood-pressure and widely dilated pupils; respiratory failure and death may follow.

In recovery from general anæsthesia the stages outlined above are gone through in reverse order.

To achieve the ideal conditions of general anæsthesia, as far as possible, the modern method is to adopt a

System of Anæsthesia

which takes advantage of the synergistic effect of a combination of hypnotic and narcotic substances. For an adult subject in good condition, the following system is frequently used:

Pre-operative Sedation. About one hour before the operation an injection of papaveretum and hyoscine (*Omnopon** and Scopolamine) is administered subcutaneously. This produces euphoria and reduces psychic trauma. It may be advisable to avoid this stage, however, if bromethol (*Avertin**) is to be used as the basal narcotic.

Basal Narcosis. This may consist of a rectal injection containing bromethol or paraldehyde; or, alternatively, the intravenous injection of a quickly acting barbiturate such as soluble hexabarbitone or *Pentothal** sodium. These measures commence the period of full narcosis and reduce the amount of maintenance anæsthetic required. Moreover they shield the patient from the discomforts of Stage II of general anæsthesia, especially the vertigo and feeling of asphyxia. When bromethol is used the patient quietly falls asleep, while the intravenous barbiturates act so rapidly that there is no appreciable twilight between consciousness and oblivion.

Anæsthesia. The narcosis initiated by methods outlined above may be maintained for hours, if necessary, by means of nitrous oxide with oxygen. To this mixture minimal ether vapour may be added should a greater degree of muscular relaxation be required. Alternatively, the nitrous oxide with oxygen mixture may be supplemented with trichlorethylene or by the continuous intravenous injection of one of the barbiturates mentioned.

Post-operative Narcosis. To quieten the patient, relieve pain and promote sleep when the effect of the anæsthetic drugs has worn off, various combinations of hypnotics and analgesics may be employed. Morphine or papaveretum are very commonly used, but there is a growing tendency to avoid them, not only because of their habit-forming character, but because of the disagreeable reactions which they may provoke. Useful alternatives to opium therapy are pethidine (*q.v.*) or:

℞	Ac. Acetylsal.	gr. x
	Barbiton.	gr. viiſs
	Sodii Bicarb.	gr. xxx.

To be taken stirred into half a wineglassful of peppermint water.

A very popular mixture in which advantage is taken of an apparent synergism between aspirin and opium is:

℞	Ac. Acetylsal.	gr. x
	Tinct. Opii	♏x
	Muc. Acaciæ	ʒſs
	Aq. Chlorof.	ad ℥ſs.

General Anæsthetics

Inhalation Group

Æther (Æther Anæstheticus, Off. Diethyl ether).

As a general anæsthetic, ether is weaker than chloroform, requiring about four times as great a concentration in the blood to produce anæsthesia. The induction time is prolonged, especially Stage II, but this may be overcome by the use of a basal narcotic. The irritant nature of ether vapour gives rise to hypersecretion of saliva and of bronchial secretion with its attendant danger of post-operative pneumonia. The pre-operative use of atropine or hyoscine by injection will reduce the amount of secretion to some extent. With ether, vomiting is very common and may be troublesome; it will occur at an early stage if the stomach should contain food; otherwise it occurs post-operatively. Tremor may appear in light anæsthesia, while a dangerous sequel is late ether convulsions, which should be treated by intravenous calcium gluconate or *Pentothal**-Sodium. It is possible that these convulsions occur mainly in those with a latent epileptic liability. Ether diminishes sugar tolerance, increases ketosis and may cause albuminuria and oligouria. It is contraindicated in diabetes, lung disease and nephritis, and alcoholic subjects are particularly resistant to it. Ether vapour with air is highly explosive. Ether is excreted unchanged by the lungs, and the rate of excretion may be accelerated by the use of carbon dioxide with oxygen, as a stimulant to the respiratory centre. Taken by mouth, ether is carminative and reflexly stimulates the medulla. In sufficient dosage it produces rapid and somewhat violent intoxication resembling that of alcohol but of shorter duration. Ether is used externally to degrease and cleanse the skin and to assist the removal of rubber adhesive plaster.

Liquor Saponis Æthereus, B.P.C.

Ethereal antiseptic soap is used for the pre-operative cleansing of skin areas, etc.

Spiritus Ætheris, Off. ½–1 fl. dr.

Spirit of Ether is used as a carminative and reflex stimulant.

Divinyl Ether (*Vinesthene**).

Divinyl ether is about four times as potent as diethyl ether, the induction phase is quicker and more pleasant and there is less gastric and respiratory irritation, and therefore less vomiting. It is non-toxic to the kidneys. It is decomposed on exposure to air and light, and only recently opened bottles should be used. It is highly inflammable. Owing to the possibility of liver damage it is safer not to use the drug for longer periods than half an hour. Convulsions have occurred.

Æthylenum.

Ethylene is an unsaturated, gaseous hydrocarbon which, combined with 10%–20% of oxygen, is an excellent anæsthetic with a wide margin of safety. The only disadvantage of the mixture is its highly explosive properties and, in consequence, its use has been abandoned in this country.

Æthylis Chloridum.

Ethyl chloride is used as a general anæsthetic for very brief operations and to induce anæsthesia which is to be continued with ether. Collapse following its use is not uncommon; this is treated along the lines described under chloroform. Methyl chloride and ethyl bromide also have been employed for similar purposes, particularly abroad. Ethyl chloride for inhalation is obtainable commercially, agreeably perfumed (with an Eau-de-Cologne type of scent) to make its vapour pleasing to the patient, especially children, and so facilitate induction. When sprayed locally its extreme volatility results in freezing of the tissues and insensibility of the nerve ends. For this reason it is used as a local anæsthetic for minor surgery, but the restoration of feeling as the anæsthetic wears off is acutely painful, and the whole procedure is now fairly generally condemned.

Chloroformum. Oral dose: 1–5 min.

The inhalation of chloroform vapour produces rapid anæsthesia and a high degree of muscular relaxation. During induction the concentration of chloroform vapour in the air intake should be about 2%; around 1% is sufficient to maintain anæsthesia. It has about four times the potency of ether as an anæsthetic, and, unlike the latter, gives rise to no irritation of the respiratory passages. The dangers inherent in chloroform narcosis arise in several ways. Sudden death in the early stage of anæsthesia may be due to stimulation of the vagal nuclei with inhibition of the heart's action; the pre-operative injection of atropine helps to prevent this from arising. Alternatively, ventricular fibrillation is a more probable cause of this sudden death. This condition is aggravated by the outpouring of adrenaline and stimulation of the sympathetic centres by afferent sensory stimuli in light anæsthesia. Apart from idiosyncrasy these early crises may be precipitated by too rapid induction. Respiratory failure may occur during administration if too high a concentration in the blood is obtained. The apnœa from respiratory depression, which occurs as a result of overdosage, acts as a physiological mechanism for the protection of the cardiac and vasomotor centres, preventing further intake of the drug. Administration of O_2 maintains the sensitivity of the centres. In the third stage, the toxic action of the drug on the myocardium may give rise to heart failure, a particularly serious complication as it renders recovery from medullary depression brought about by the drug much more uncertain. This is more likely to happen in cases of pre-existing cardiac weakness, fatty degeneration, etc. Chloroform almost always produces some temporary degree of liver dysfunction, and its use should be preceded, when possible, by the administration of dextrose for a day or two, to tide the patient over the acidotic period which would otherwise result. An increased calcium intake, to decrease the permeability of the liver cells, is also an advantage. Delayed chloroform poisoning sets in, one to four days after the operation, and is due to pathological changes in the liver. It is characterised by jaundice, vomiting, delirium, coma and death. It is especially to be apprehended with children and after prolonged administration of the anæsthetic.

Cardiac failure in the course of chloroform and other anæsthetics may be **primary** (ventricular fibrillation and cardiac asystole excited reflexly) or **secondary** to asphyxia with respiratory failure, the former being the more dangerous. Treatment necessitates establishing a clear airway, tilting the patient into the Trendelenburg position, rhythmic inflation of the lungs with oxygen and carbon dioxide mixture or artificial respiration. Lobeline or other respiratory stimulants should be used. In primary cases, or where the above measures fail in secondary cases, it is necessary to inject 10 ml. of 2% procaine intracardiacally if there is ventricular fibrillation and, if auricular puncture fails, to resort to cardiac massage. Intracardiac injection of Solution of Adrenaline has been used to remedy heart-block and cardiac arrest, but ventricular fibrillation may result, or be intensified if already present. It should, however, be employed if cardiac massage fails. Methedrine (*q.v.*) may be used if the blood-pressure falls markedly during the operation. The advantages of chloroform over ether are quick induction, lack of respiratory and gastric irritation, and non-explosive nature of the vapour, but it is rarely used alone because of its toxicity and it may be entirely ousted by trichlorethylene (*q.v.*).

Taken by mouth, chloroform in dilute aqueous solution is warming and carminative. Applied externally it is rubefacient.

Aqua Chloroformi, Off. ½–1 fl. oz.

A vehicle for mixtures possessing antiseptic properties against bacteria and moulds, and used as a carminative and "sweetening" agent.

Linimentum Chloroformi, B.P.C.

This preparation, which contains camphor also, is used to unbroken skin as a stimulating embrocation.

Spiritus Chloroformi, Off. 5–30 min.

This is used as a preservative and corrective in mixtures; it is also carminative.

Tinctura Chloroformi et Morphinæ, B.P.C. (Chlorodyne), 5–10 min.

This preparation contains a trace of morphine and of hydrocyanic acid with chloroform and peppermint. It is prescribed as a carminative and mild cough sedative. Chlorodyne is a traditional domestic remedy for varied minor ailments, and cases of addiction to it are not unknown. Addicts are liable to liver damage and fatty degeneration of the heart as a result of chronic chloroform poisoning.

Cyclopropanum (*Trimethylene*).

Cyclopropane, a colourless gas with a characteristic smell, is a very potent anæsthetic. A concentration of only 10%–20% of cyclopropane in oxygen gives rise to full surgical anæsthesia. It is exhaled quantitatively and must be administered in a closed-circuit apparatus with soda-lime to absorb the carbon dioxide also exhaled. The large proportion of oxygen with which it may be combined renders cyclopropane a very safe anæsthetic in experienced hands and, being non-irritant to the lungs, it is of particular value in respiratory diseases, in thoracic surgery and also in shock. Its chief disadvantages are that the cyclopropane-oxygen mixture is explosive and that it is depressing to the respiratory centre. For this reason heavy premedication is to be avoided. Cyclopropane raises the blood-pressure and may cause cardiac irregularities by increased irritability of the heart muscle; these symptoms will be aggravated if adrenaline is used to combat the respiratory depression. It gives rise to neither liver nor renal damage and, altogether, is probably the least toxic of the powerful anæsthetics.

Nitrogenii Monoxidum.

Nitrous oxide (laughing gas) is a colourless, odourless gas with useful anæsthetic properties due to a specific depressant action on the brain. It is used in dental and other minor surgery to produce "asphyxia anæsthesia" for periods of 30–60 seconds. Mixtures consisting of nitrous oxide with at least 10% of oxygen to prevent serious anoxæmia may be used to produce light anæsthesia for prolonged periods in many types of operation. Full muscular relaxation cannot, however, be obtained with so high a proportion of oxygen present, and where necessary some system of combined anæsthetics such as is mentioned in the introduction to this chapter must be employed. Nitrous oxide and oxygen mixture possesses the advantage over the cyclopropane mixture of being non-explosive. Nitrous oxide is exhaled quantitatively and, in suitable "close-circuit" apparatus, the patient continues to rebreathe the same gas; additional oxygen only is required, while the carbon dioxide exhaled may be taken up by soda-lime. Nitrous oxide is non-irritant to the respiratory passages, produces a rapid induction and is non-toxic.

In the second stage of labour, mixtures of nitrous oxide with 20% or more of oxygen may be used to produce "amnesia-analgesia"; a special type of apparatus (McKesson) may be used which prevents the concentration of nitrous oxide exceeding a certain fixed level. In this country the Minnitts apparatus supplying 60% of nitrous oxide and 40% of air is most commonly employed in obstetrics and is recognised as being suitable for use by midwives.

Trichloroethylenum, Off. (*Trilene**).

Trichloroethylene is a heavy, non-inflammable liquid of relatively low volatility which is used as a general anæsthetic and as an inhaled analgesic. It is non-irritant to the respiratory passages and its vapour is non-explosive. Cardiac irregularities arising from trichloroethylene anæsthesia have been noted, but it is much less toxic to the heart than chloroform. Induction is more rapid and more pleasant than with ether. During anæsthesia polypnœa is frequent, and is a disadvantage, and there may be some instability of blood-pressure. Its anæsthetic potency is greater than that of ether but less than that of chloroform, and muscle relaxation is not always complete. For this reason the concurrent use of nitrous oxide and oxygen mixture, or of ether, may be necessary, especially in abdominal surgery. Owing to the low volatility of trichloroethylene it must be vaporised for anæsthetic purposes by passing a current of air or of oxygen through the liquid in a vaporising bottle.

Trichloroethylene is a powerful and useful analgesic for use by inhalation. For purely analgesic purposes the anæsthesia need not proceed beyond the first phase, the patient retaining consciousness. So employed, the drug has proved of value in controlling trigeminal and other neuralgias in obstetrics and in *angina pectoris*. It may be used also in orthopœdics to minimise pain in minor manipulations; similarly "painful dressings" can be performed with a minimum of discomfort to the patient. For these purposes the drug is supplied in cloth-covered ampoules or can be given with the aid of a vaporising bottle as described above. Trichloroethylene is used externally to degrease the skin and cleanse dirty wounds, etc. A temporary trigeminal nerve paralysis has been noted as a complication of trichloroethylene anæsthesia. This may take some time to wear off. It has been shown recently that toxic decomposition products may be formed if trichloroethylene is used in a closed circuit apparatus.

Intravenous Anæsthetics

The rapidly acting barbiturates, such as *Pentothal** sodium, are commonly used intravenously:

1. As basal narcotics, as mentioned in the introduction to this chapter.
2. To maintain general anæsthesia.

Used as basal narcotics they are injected slowly until consciousness is lost; there is considerable variation in the dose required to produce unconsciousness. Administered in this way, induction occupies only a few seconds and anæsthesia persists for about fifteen minutes. This is suitable for short operations, particularly oral and facial, and for examinations such as cystoscopy and sigmoidoscopy. If it is desired to maintain general anæsthesia with the barbiturate then, following induction, further small doses of the drug can be injected as required; alternatively, the drug can be added from time to time to an intravenous saline infusion. Probably the best method of all is to maintain a light level of anæsthesia with nitrous oxide and oxygen mixture, and to administer small repeated doses of barbiturate intravenously to maintain adequate muscular relaxation. These drugs require very skilled handling, and although safe enough in the hands of experts, it must be stressed that fatalities may be expected from inexperienced handling, especially in unsuitable cases. The administration of oxygen during the anæsthesia is of advantage. The anæsthetic barbiturates are medullary depressants, and the fall in blood-pressure and respiratory depression may be considerable in overdosage. Laryngospasm may occur during light anæsthesia and may be precipitated by the introduction of an oral airway and laryngoscope and can be relieved by the intravenous injection of 5–10 mg. *d*-tubocurarine. When these drugs are correctly used there are usually no undesirable after-effects, but occasionally, especially in the case of children, there may be transient excitement or even mania. Amnesia for some hours is the rule, and may be attributed to the effect on the cortex of the substances resulting from the initial breakdown of the anæsthetic barbiturate within the tissues. Patients sometimes relapse into unconsciousness after a transient recovery from the anæsthetic effect. Nausea and vomiting may occur but are not common, and it is possible that this reaction may be psychogenic or result from the associated use of morphine, as it is difficult to correlate nausea with any direct effect of the anæsthetics themselves. Other sequelæ occasionally met are prolonged drowsiness, headache and photophobia. Agranulocytosis and toxic jaundice have been noted, and with children mental changes following the use of soluble hexabarbitone have been described. Tissue necrosis, if any of the solution gets outside the vein during injection, and even venous thrombosis may occur as a result of the unavoidable alkalinity of the soluble sodium derivates which are employed.

Since they give rise to no pulmonary irritation these anæsthetics are useful in most cases where anæsthesia is complicated by a chronic respiratory condition; they are useful also when the diathermic cautery is to be used. The intravenous barbiturates are **contraindicated:**

1. In cases of hepatic disease, particularly with jaundice, as liver damage may ensue. In any case, hepatic efficiency is necessary because it is by the liver that these drugs are detoxicated.
2. In patients with severe heart or lung embarrassment.
3. In cases of suppuration in the neck or throat.

Apart from their employment as anæsthetics, the intravenous barbiturates are used as anticonvulsants, especially in strychnine poisoning and tetanus, and for narco-analysis in psychiatry. They have also been employed rectally, in small repeated doses, to promote amnesia-analgesia in childbirth.

Hexobarbitonum Sodium (*Evipan**-Sodium).

Soluble hexobarbitone occurs as a white powder which is packed in ampoules containing 0·5 gramme and 1 gramme respectively. It is employed as a 10% solution, the powder being freshly dissolved in the appropriate volume of sterile water at the time of injection. The solution is clear and colourless, and has a strongly alkaline reaction. It may give rise to twitching during the induction period. **Antidotes** to hexobarbitone are applicable, also, to all cases of barbiturate poisoning; they include inflation of the lungs with oxygen and carbon-dioxide mixture, the intravenous injection of nikethamide or picrotoxin and lumbar puncture. (See also the monograph on Barbitone.)

*Pentothal**-Sodium.

*Pentothal**-sodium is a pale yellow powder, which is supplied in 0·5 and 1 gramme ampoules. It is used as a 5% solution in sterile water, the solution being made freshly for injection. The solution is clear, yellow in colour and has an odour of hydrogen sulphide. The molecule contains sulphur which, during detoxication of the drug, is liberated in a reactive condition. *Pentothal** must not, therefore, be used on patients receiving treatment with any of the sulphonamides owing to the danger of sulphæmoglobinæmia. *Pentothal**-sodium is less liable to cause twitching than soluble hexobarbitone, and it produces better relaxation and longer anæsthesia than the latter. In cases of poisoning the antidotes mentioned in the preceding monograph should be employed.

*Kemithal Sodium** (Sodium cyclohexenyl-allyl-thiobarbiturate).

This compound is used as an intravenous anæsthetic in doses (induction) of 0·5–1·5 gm. It is claimed to have a relatively high safety factor.

Anæsthetics acting by paralysing Skeletal Muscles

Curare.

This is the South American arrow poison extracted from various plants. It has the property of paralysing skeletal muscles, and has been recently employed in surgery to produce muscular relaxation as an adjunct to general anæsthesia. Commercially, two preparations are available for this purpose, one amorphous and the other crystalline, both depending on *d*-tubocurarine chloride for their activity. The amorphous preparation is called "Intocostrin" and has about a quarter of the activity of the crystalline one, pure *d*-tubocurarine chloride **Intocostrin** is physiologically standardised to contain 20 units or mg. of curare extract per ml., and is prepared from *chondodendrum tomentosum*, a vine.

d-tubocurarine chloride (*Tubarine**).

This preparation is preferred in this country as its potency is more reliable. The crude extract from which it is prepared is imported in bamboo tubes, "tube curare." In man, 1 unit of intocostrin is equivalent to 0·3 mg. *d*-tubocurarine.

Curare has no action by mouth as it is detoxicated in the liver after absorption from the alimentary tract. If injected subcutaneously its action appears in 20 minutes, if intravenously in 10 seconds, maximal in 3 minutes. Apart from detoxication of the liver, some is excreted by the kidneys. Skeletal muscles are paralysed as a result of the drug blocking nerve impulses at the myoneural junctions, probably preventing a receptor substance in voluntary muscle from reacting to acetylcholine. Thus the drug acts anywhere in the nervous or muscular systems where acetylcholine is the chemical mediator. Curare also blocks synaptic transmission between pre- and post-ganglionic sympathetic fibres, as well as peripheral response to vagal stimulation, probably as a result of similar prevention of the receptor substance from reacting to acetylcholine. Physostigmine and *Prostigmine** antagonise the action of curare by preventing the neutralisation of acetylcholine by cholinesterase, thus allowing cumulation of excessive amounts of acetylcholine, which acts on the receptor substance and overcomes its inhibition by curare. If given to a conscious person, 10 mg. *d*-tubocurarine chloride causes partial paralysis of face, neck, larynx, limbs and intercostals, in that order, with ptosis and strabismus, the effect passing off in ½ hour. With 30 mg. the paralysis is complete, and there is inability to speak or move. Rapid, shallow breathing, terror and commencing loss of consciousness occurs. Artificial respiration and oxygen can prevent asphyxia. Symptoms persist for about 6 hours. *d*-tubocurarine chloride in therapeutic doses has no toxic action on the heart, but adequate oxygenation is necessary to prevent myocardial deterioration, particularly if there is heart disease. The blood-pressure may rise for a few minutes as a result of CO_2 cumulation and emotional reaction. Very large doses may cause a fall in blood-pressure, apnœa and loss of consciousness.

It is because of their paralysing effect on skeletal muscles that curare drugs are employed to produce muscular relaxation in abdominal and thoracic operations. The action on the autonomic system, particularly with larger doses, is of importance in anæsthesia, because the depression of the laryngeal and bronchial reflexes prevents spasm and intra-tracheal intubation is facilitated. There may be either contraction or relaxation of stomach and intestines; relaxation is more likely if barbiturates are used in conjunction with curare. Satisfactory relaxation for abdominal operations may be obtained with *d*-tubocurarine chloride by administering a dose of 2–2·5 mg. per stone body-weight intravenously, after the patient has been stabilised in the second plane of anæsthesia with a general anæsthetic like *Pentothal,** gas and oxygen. Care must be taken in selecting the correct dose or respiratory depression occurs, and there is small margin between an adequate and an overdose. To avoid this risk, it is suggested that dosage should be based on the reaction to an initial small dose rather than on a dose/weight ratio. The average adult dose is 10 mg. *d*-tubocurarine chloride or 40–60 mg. intocostrin. For operations lasting longer than ½–1 hour, a second injection of half the first is given intramuscularly ½ hour after the first and will produce adequate relaxation for 1½–2 hours. Longer operations require further injections of a quarter the first dose from time to time. Old people require an initial dose of 10 mg., and children up to 12, one of 6 mg. The curarinised patient has breathing characterised by a pushing out of lower chest and abdomen together with a jaw and tracheal tug with each diaphragmatic contraction, and the lungs are easily inflated by pressure of the rebreathing bag (controlled breathing). The chief danger lies from respiratory depression and arrest, but this can be overcome by controlled breathing and the drug is easily eliminated. Death has, however, occurred. Special care is necessary with patients in the Trendelenburg position, which interferes with vital capacity. Post-operative complications are said to be less than with spinal and general anæsthesia, and other advantages claimed are the ease of administration, the absence of shock and rapidity of recovery after anæsthesia. Because it reduces the amount of general anæsthetic required it is valuable in poor risk patients with peripheral circulatory failure.

Contraindications: (1) It should not be given by the inexperienced anæsthetist. (2) It should not be used with cyclopropane in abdominal operations, as excessive gut contraction may be caused. Great care must be exercised in intestinal obstruction, renal damage and lung abscess.

Other uses of curare: (1) Intravenous injections are given to reduce the risk of fracture in convulsive therapy, particularly in the old. (2) In spastic states, *e.g.* tetanus, *status epilepticus*, infantile spastic paralysis, *paralysis agitans*, Huntington's chorea, the action of the drug may be prolonged and side effects like diplopia, blurred vision and weakness reduced by intramuscular administration of the drug in a mixture of arachis oil and white wax. American clinicians have advocated its use in the acute stages of poliomyelitis, so as to relax the antagonists of the paralysed muscles, which antagonists they maintain are in a state of spasm and responsible for deformities.

*Myanesin.**

*Myanesin,** α-β-dihydroxy-γ-(2-methylphenoxy)-propane belongs to the class of α-glycerol ethers. It is a new synthetic drug, which on intravenous injection produces abdominal relaxation without intercostal paralysis. Its action appears to be due to depression of spinal cord reflexes or motor pathways in the basal ganglia. It is rapidly destroyed in the body. Unfortunately intravascular hæmolysis with hæmoglobinuria and renal failure makes the present compound unsafe.

Administration: 5–10 ml. are given intravenously a few seconds before opening the peritoneum and abdominal relaxation occurs in a few seconds. In long operations this dose can be repeated as often as required.

Basal Narcotics

The introductory remarks to this chapter should be consulted, together with the section dealing with intravenous anæsthetics.

Drugs commonly employed as basal narcotics are:

Barbiturates.
Bromethol.
Paraldehyde (*q.v.*).

Barbiturates.

Hexobarbitone-soluble (*q.v.*).
*Pentothal**-sodium (*q.v.*).

Pentobarbitone Sodium (*Nembutal**).

Pentobarbitone sodium can be given intravenously as a freshly prepared 10% solution in sterile water, orally in capsules, or rectally, usually in suppository form. The adult dose is 3–4½ grains, 1½ hours before operation, and for children 2 grains may be given rectally in suppository form, 3 hours before the operation. This time-lag must be attributed to the cocoa-butter of the suppository base hindering absorption, as in aqueous solution the drug diffuses very rapidly from the rectum. It is also used in the relief of labour pains. In addition to its action as a basal narcotic the drug, in small doses, is used as a simple hypnotic, useful because there is no "hang-over." Larger doses are employed in the treatment of tetanus and strychnine poisoning. Idiosyncrasy to the drug may result in urticarial skin eruptions, and even fatal liver damage.

Bromethol, Off. (*Avertin**).

Bromethol consists of a solution of tribromoethyl alcohol in tertiary amyl alcohol (amylene hydrate). The dosage for adults is 0·09 to 0·12 grammes per kilo. body-weight, the higher dosage being used in cases where the metabolic rate is high. In obstetrics the dosage is 0·075 grammes per kilo. For adults, bromethol is used only as a basal narcotic because the large dosage required to maintain anæsthesia is unsafe. Children, other than very undersized or wasted subjects, tolerate the drug well. The dosage for children is 0·175 grammes per kilo., and if premedication with morphine or hyoscine is adopted, and a field block employed, no other anæsthetic is required in about 75% of cases.

The dose is given per rectum freshly dissolved as a 2½% solution in warm distilled water. To the solution a few drops of Congo-red solution are added, and no trace of blue colour must develop. A blue coloration indicates decomposition of the tribromoethyl alcohol with the production of acetaldehyde and hydrobromic acid, and the use of such a solution would give rise to acute proctitis.

When a suitable solution is injected rectally maximal concentration of the anæsthetic in the blood occurs in half an hour.

Bromethol is detoxicated in the liver and excreted by the kidneys; elimination takes 48 hours. The drug depresses the respiratory centre and lowers body temperature. It is safe to the heart and usually safe to the liver, but jaundice and severe liver damage have been described. Diarrhœa due to irritation of the rectal mucosa may occur. Bromethol being non-irritant to the respiratory tract is a useful anæsthetic for bronchitics and asthmatics. It is used also in cranial and eye surgery and under tropical conditions where ether is at a disadvantage. It is thought to be antagonistic to thyroxine and is commonly employed in thyroidectomy operations. Bromethol is used therapeutically in strychnine and tetanus convulsions, in eclampsia, *status epilepticus*, in acute delirium, including that of alcohol, and in severe chorea. It is **contraindicated** in subjects having a low blood-pressure, a low metabolic rate, and those with kidney or liver diseases or colitis. **Antidotes:** Oxygen with carbon-dioxide mixture, ephedrine subcutaneously, the high rectal injection of hypertonic solution of sodium thiosulphate, nikethamide, picrotoxin or strychnine parenterally.

Local Anæsthesia

Local anæsthesia (or analgesia) can be produced in the following ways:

1. **Surface anæsthesia,** *i.e.* application to the surface of the skin or mucous membrane.
2. **Infiltration anæsthesia,** comprising injection subcutaneously or into the deeper planes.
3. **Regional block,** injection into or around nerve trunks or roots.
4. **Epidural injection,** into the epidural space around the spinal nerves. A special type of this is a **caudal block,** in which the injection is made through the sacral hiatus around the lower spinal nerves and is used for perineal operations and also continuously for the abolition of labour pains.

5. **Intrathecal Injection** (Spinal Anæsthesia).

Solutions of spinal anæsthetics can be **hyperbaric**; the solution having a greater density than that of the cerebrospinal fluid. Examples are: Amylocaine (*Stovaine**), 10%, and heavy *Nupercaine,** 0·5% in 6% dextrose.

Isobaric solutions are those having the same specific gravity as the cerebrospinal fluid, *e.g.* buffered and isotonic 0·5% *Nupercaine,** 1% *Pantocaine.** As the cerebrospinal fluid varies, however, it is not always possible to be certain of the isobaric nature of the anæsthetic solution.

Hypobaric solutions are those having a lower specific gravity than that of the cerebrospinal fluid, *e.g.* light *Nupercaine** 1 : 500 in 0·5% saline.

These various solutions are suitable for high or low blocks according to the amount injected and the position in which the patient is arranged on the operating table. In the case of all the spinal anæsthetics the sensory and the sympathetic nerves are blocked before, and recover after, the motor nerves. Anæsthesia occurs within a few minutes of injection and persists up to two hours.

Indications for Spinal Anæsthesia.

Spinal anæsthesia is used mainly for operations below the diaphragm in patients who are not shocked and are suffering from, or liable to, complications of the respiratory passages. Bladder and rectal operations in particular call for spinal anæsthesia and it is used also in cases of paralytic ileus. It is used therapeutically in the treatment of megacolon, temporarily to paralyse the sympathetic nerve supply. Such relief may be transient only, but the treatment will indicate whether the case is suitable for sympathectomy. The same procedure may yield sufficient improvement in the blood supply in cases of *thromboangiitis obliterans*, by production of vasodilatation following sympathetic paralysis, to warrant sympathectomy. Continuous spinal anæsthesia is becoming increasingly popular in the United States, the needle being left *in situ* in the subarachnoid spaces, and additions of the anæsthetic (generally procaine) made from time to time. Recently spinal anæsthesia has been employed to combat renal failure in Weil's disease by relaxing the spasm of the glomerular vessels responsible for the diminished urinary output. The blood-pressure must be maintained by injecting *Methedrine** or other similar compound.

Contraindications for Spinal Anæsthesia.

This procedure is contraindicated in shock and other states of low blood-pressure, in vertebral diseases including abscess, and in children.

Toxic Symptoms with Spinal Anæsthetics.

Collapse with marked fall in blood-pressure may be treated by the intramuscular injection of s. methylisothiourea (2 ml. of 10% solution), ephedrine, *Pholedrine** or *Methedrine,** and by oxygen with carbon-dioxide mixture. The last mentioned is used also in cases of failure of respiration. Other untoward reactions are: headaches, vomiting, hyperpyrexia, retention of urine, transient and, sometimes, permanent paralysis, the last mentioned is particularly liable to occur with amylocaine.

Amylocainæ Hydrochloridum (*Stovaine**), ⅓–1½ gr. intrathecally.

Amylocaine is one of the synthetic anæsthetics. It should be used only for spinal anæsthesia as, injected locally, it is irritant and dilates the blood-vessels. It is generally used as a hyperbaric solution, 10% of the drug in a solution containing 10% of either sodium chloride or of dextrose.

Benzocaina (*Anæsthesine**), 5–10 gr. orally.

Benzocaine possesses useful anæsthetic properties when applied in powder form to mucous or ulcerated surfaces. It is used internally to relieve the pain of gastric neoplasm, and as an insufflation in tubercular laryngitis. Starch containing up to 50% of benzocaine is used as an analgesic dusting-powder, and the following ointment may be applied to small painful burns and to allay pruritus or the pain of herpes zoster:

℞	Benzocain.	7½%
	Eucalyptol. Menthol.	āā 5%
	Adep. Lanæ Hyd.	25%
	Paraff. Molle	ad ℥

m. ft. unguent. pro applicat.

A similar local anæsthetic to the above is butyl-*p*-amino benzoate or butoform (*Butesin,* Scuroform**), used as a powder, alcoholic or oily solution, ointment or suppositories. Other local anæsthetics suitable for infiltration or surface application are *Metycaine,** a propyl benzoate derivative, and *Panthesine,** a *p*-aminobenzoic acid derivative.

Benzamina Hydrochloride (*Beta-Eucaine**).

This substance, chemically allied to cocaine, is used as a local anæsthetic. For surface application 1–12%, for injection 0·1–5%. Similar preparations are benzamine lactate and benzamine borate (*Borocaine**), used as surface anæsthetics (0·2–5%).

Amethocainæ Hydrochloridum, Off. (Tetracaine hydrochloride, *Decicaine,* Anethaine,* Pantocaine**).

This synthetic body is commonly used as a surface anæsthetic in 1% solution. It is about ten times more active than cocaine and only three times as toxic; it is therefore widely used as an alternative to cocaine solutions for producing surface analgesia, but local reactions due to idiosyncrasy may occur. A 1 : 1000 solution in normal saline, to which a few drops of adrenaline solution should be added, is used for infiltration.

Cinchocainæ Hydrochloride (β-diethylaminœthylamide of 2-butyloxycinchonine hydrochloride).

This is an effective surface anæsthetic suitable for local as well as for intrathecal injections. It has a more powerful and prolonged action than cocaine, but is much more toxic. A 1–2% solution is suitable for anæsthesia of the mouth, ears, nose or throat, whilst a 0·1% solution is employed for ocular or urethral anæsthesia. For intrathecal injection either 1 in 1,000 or 1 in 5,000 in isotonic saline or dextrose solution is used, the dose administered varying from 0·005–0·01 gm. For local infiltration 0·1–0·2% solutions are used, the dose not exceeding 0·02 gm.

Cocainæ Hydrochloridum, ⅛–¼ gr.

The soluble salts of cocaine are rapidly absorbed from the nasal mucosa and from the rectum, or following parenteral injection. Oral administration is less effective and is only employed when a local sedative or analgesic action on the gastric mucosa is required. After absorption, there is generally marked euphoria due to stimulation of the sensory cortex, and what is sometimes called a raised "anxiety threshold." The exhilaration produced is followed, however, by a trough of depression, and addiction to the drug is readily acquired. In larger doses garrulity is common, followed by hallucinations. The stimulation spreads to the motor areas of the brain, and restlessness, tremor and, in sufficient dosage, convulsions occur. Pallor, profuse perspiration, arteriolar constriction with raised blood-pressure, and mydriasis occur and may be due to stimulation of the sympathetic centres. The peculiarly marked disorders of conduct which cocaine may produce are explained by the fact that depression of the frontal centres which govern behaviour occurs while the lower centres are still in a state of stimulation. Much less marked, but similar in type, is the effect on the brain of atropine, which is closely related to cocaine in chemical structure. At first, if the dose of cocaine be small, there is increased resistance to fatigue, but this is transient, and increasing dosage produces ineptitude. Addiction to the drug involves complete moral and physical degeneracy. Cocaine is especially individual in the type of reaction it produces most prominently; in some cases marked anxiety rather than euphoria develops very rapidly after the drug has been taken. Idiosyncrasy of a dramatic character is occasionally met, a small dose producing faintness, collapse and, possibly, respiratory failure. Cocaine must never be used intravenously, and it is a wise precaution to make a subcutaneous injection not exceeding $\frac{1}{8}$ gr. to test the patient's response before it is used as a local anæsthetic.

Permeation anæsthesia of mucous surfaces is effected with a 5% solution of cocaine hydrochloride containing 1 : 2,000 of adrenaline, applied on strips of gauze. Stronger concentrations are sometimes used, but the patient's reaction should be ascertained previously. Anæsthesia of the larynx may be obtained by spraying with a solution of cocaine. Solutions containing 2–4% of the hydrochloride are applied to the eye to blanch the conjunctiva and produce mydriasis; these effects are probably produced by stimulation of the sympathetic nerve ends. Anæsthesia is produced also, of course, but in cases of injury to the eye atropine is preferable, since its anæsthetic effect, although milder, is more prolonged, and cocaine, by restricting the blood supply, has a deleterious effect on the wound. Cocaine is now seldom used for infiltration; for this purpose it has been almost entirely superseded by procaine and other synthetic substances. Cocaine solutions are sometimes used locally to relieve laryngitis and pharyngitis, and to anæsthetise the urethral mucosa prior to catheterisation or cystoscopy. This procedure can be highly dangerous, however, since if trauma occurs considerable absorption of cocaine may take place. Although cocaine solutions are occasionally recommended for local application by means of a spray for the relief of hay fever and asthma, the obvious danger of addiction is sufficient to condemn such therapy. Cocaine ointment is employed to allay the pain of shingles and of intractable pruritus,but amethocaine (*q.v.*) provides an effective alternative.

Guttæ Cocainæ, B.P.C. (Factory Eye Drops).

Cocaine 0·5%, with mercuric chloride in castor oil.

Lamella Cocainæ, Off.

Small discs of gelatin for ophthalmic use, each containing $\frac{1}{50}$ gr. of cocaine hydrochloride.

Oculentum Cocainæ, B.P.C.

An eye ointment containing 0·25% of cocaine hydrochloride.

Unguentum Cocainæ, B.P.C.

Contains 4% of cocaine.

*Nupercaine** (*Percaine**).

This synthetic quinoline derivative is widely used in spinal anæsthesia in doses of 7·5 to 10 mg. of 1 in 200 solution. It is exceedingly powerful, its potency being about forty times that of procaine and of about twenty-five times the toxicity. Its anæsthetic action is prolonged and solutions (1%–2%) are very effective for surface analgesia. Infiltration with solutions containing 1 : 2,000 up to 1 : 500 is practised, but *Nupercaine** is often regarded as too toxic for this purpose. The compound is extremely stable, and solutions can be repeatedly boiled for sterilisation.

Orthocaina (*Orthoform**).

Orthocaine resembles benzocaine in being a meagrely soluble, white powder which is applied as an analgesic to abraded surfaces; it is insufflated for the relief of pain in tubercular laryngitis. Orthocaine has a decided antiseptic value, but it may give rise to some necrosis at the site of application. Ointments containing 5%–10% are applied to relieve the pain of anal fissure and hæmorrhoids.

Phenacainæ Hydrochloridum, U.S.P. (*Holocain**).

This salt, in 1% solution, is occasionally used as a surface anæsthetic in ophthalmology; 2–5 drops being instilled into the eye. It is not suitable for injection.

Procainæ Hydrochloridum (*Novocaine,* Planocaine,** etc.).

Dosage:—Orally: ½–2 gr. **Subcutaneously:** up to 15 gr. **Intrathecally:** up to 2½ gr.

Procaine is a synthetic substance bearing some structural resemblance to cocaine, which is widely used for the production of local anæsthesia by injection. Unlike the salts of cocaine, it exerts only a feeble superficial anæsthetic action to mucous surfaces and, so applied, its penetrative powers are small. It is much less toxic than cocaine and lacks the vasoconstrictor action of that drug. When injected, therefore, its anæsthetic effect is very transient unless it is combined with adrenaline, which, by vasoconstriction, localises the action. In practice this combination is almost universally employed. Another important difference between procaine and cocaine is that the former exerts no high cerebral effect and is not a drug of addiction. Care must be taken not to allow procaine to get into a vein during injection as it depresses the vasomotor centre and may produce a sudden fatal fall in blood-pressure. For infiltration ¼%–½% solution in normal saline is used; for nerve trunks 1%–2% is employed, while intrathecally a 5% solution in 5% solution of dextrose is usual; sometimes to the latter strychnine hydrochloride is added to help maintain the blood-pressure (*Spinocaine**). In the treatment of severe burns or of marked pruritus, *e.g.* from jaundice, procaine, 1 gm. in 1 litre of normal saline, can be given by slow intravenous drip and can be repeated for several days.

Where it is desired to produce a prolonged anæsthesia (lasting for a week or more) as happens, for example, after operation for the removal of hæmorrhoids, in cases of *pruritus vulvæ*, anal fissure, sprains, fibrositic areas, amputation stumps, *herpes zoster*, etc., procaine in oily solution is injected and slow continuous absorption takes place. A similar technique is employed in suitable cases of neoplasm. *Proctocaine** containing procaine, benzyl alcohol, and butyl *p*-aminobenzoate in a bland oil typifies such an injection.

Another preparation is procaine borate (*Borocaine**) which is stated to exert definite surface analgesia.

ENDOCRINE SUBSTANCES

PREPARATIONS containing the secretions from a number of the ductless glands have been dealt with under other headings. There remain to be considered preparations derived from the internal secretion of the pancreas and from the thyroid and parathyroids.

Insulinum, 5–100 units, subcutaneously.

Insulin, a hormone secreted by areas of differentiated tissue in the pancreas, which are termed the Islets of Langerhans, is prepared commercially from mammalian pancreas. All samples of insulin are standardised by determining the amount which will produce the same fall in the blood-sugar level in a group of 2 kg. rabbits as is produced by one international unit (present in 0·05 mg. of an international crystalline preparation).

The action of insulin is first and foremost upon carbohydrate metabolism. It converts dextrose in the blood into glycogen, which is stored in the liver and muscles. A rise in blood sugar after a meal stimulates insulin production with the subsequent fall in blood sugar to normal levels. The muscles, in doing work, burn up these glycogen reserves. The normal metabolism of fat and of protein is apparently dependent upon this regulation of carbohydrate metabolism by insulin. Fats are eventually oxidised in the tissues to carbon dioxide and water, but if carbohydrate metabolism is imperfect (as in diabetes) fat oxidation is incomplete, and toxic products of incomplete fat metabolism accumulate within the tissues and appear in the urine. These products include β-hydroxybutyric acid, diacetic acid and acetone; they exert a cerebral toxic action, etc., and the condition is termed, clinically, ketosis. In severe ketosis a further complicating factor is the loss of alkali from the tissues following neutralisation of the acidic bodies produced. A vicious circle in fact occurs, since the tissues, unable adequately to metabolise fat except under normal conditions of sugar metabolism, **endeavour to burn even more fat** to obtain the calories ordinarily available to them by combustion of dextrose. A further complication is that fat combustion makes greater demands upon the oxygen supply to the tissues than does the metabolism of dextrose, and this factor, **in itself,** tends to give rise to the presence of the products of uncompleted fat metabolism. Protein metabolism, also, is upset in severe diabetes, and there occurs an excessive breakdown of protein with the formation of sugar and ketones. When the islets are diseased, as in *diabetes mellitus,* insulin is not secreted in adequate quantity and the regulating mechanism, outlined briefly above, becomes ineffective. There results accordingly a high blood-sugar level (hyperglycæmia) and ketosis. When the ketosis becomes marked, diabetic coma sets in. These ill-effects can be controlled by the administration of insulin in suitable dosage. The doses employed must be large enough to restore the blood sugar to normal levels when coupled with the minimal carbohydrate intake compatible with health, and to cause the disappearance of sugar and acetone from the urine. Insulin is given half an hour before a meal once, twice or, rarely, thrice daily to ordinary diabetics. When the condition has been brought under control the patient is standardised on the minimum dosage which, coupled with dietetic measures, will enable him to avoid ketosis and maintain reasonably normal blood-sugar levels; this is called the maintenance dosage. In cases of coma, however, insulin must be given in large doses (30–100 units) four-hourly or even more frequently, depending on the response. In coma the first dose of insulin is often given intravenously. Insulin overdosage is followed by an excessive fall in the blood-sugar level (hypoglycæmia) with symptoms such as weakness, tremors, sweating, confusion, apprehension palpitations and hunger pains. If the fall in blood sugar is great, coma (insulin, or hypoglycæmic coma), convulsions and palsies may develop. This coma may of itself prove fatal, or, if prolonged, give rise to a psychotic state. Hypoglycæmia can, also, precipitate anginal attacks in patients with coronary disease. Hypoglycæmia can be relieved by oral sugar (about half an ounce), or in coma by an ounce of dextrose in 10%–20% solution intravenously or by œsophageal tube. Adrenaline Solution (1 : 1000), 1 ml., or Injection of Posterior Pituitary, 1 ml., injected intramuscularly raise the blood sugar by mobilising glycogen reserves, and should be given at once in cases of insulin coma. Local reaction to insulin injection may be a stinging sensation produced by acidity of the solution or brawny swellings of an allergic type, or take the form of either thickening or atrophy of subcutaneous tissues.

Insulin, in small dosage, has been used with oral dextrose in cases of malnutrition. Hypoglycæmic shock produced by large doses of insulin is sometimes used in the treatment of schizophrenia. The treatment is dangerous, but considerable benefit may result in some cases.

Ordinary insulin (soluble insulin) is available commercially as

"Single Strength"	20 units per ml.
"Double Strength"	40 ,, ,,
"Quadruple Strength"	80 ,, ,,

The last mentioned is only employed where large doses have to be given. The duration of action of soluble insulin depending on the dose is from 6 to 12 hours.

Zinc Protamine Insulin.

Protamines are proteins derived from the sperm of fish. Zinc protamine insulin is a suspension of insulin made by adding a trace of zinc to a combination of protamine with insulin. Medication with zinc protamine insulin is a type of depot therapy because mobilisation of soluble insulin from the injection is spread over a period of perhaps 24 hours or more if doses of over 30 units are used. This has the advantage of lessening the frequency of injection in moderately severe cases. In more severe cases, however, the slow action renders zinc protamine insulin unsuitable alone, since it does not provide adequate control during the early stages of the injection. In such cases it is necessary to give a dose of soluble insulin for more immediate action, with the dose of zinc protamine insulin. It is commonly the practice to give this combined dose in the morning and, if necessary in more severe cases, a second dose of soluble insulin in the evening. Some clinicians, however, prefer, in these severe cases, to give the combined dose in the evening and soluble insulin alone in the morning. The soluble insulin is drawn up in the syringe first, followed by the zinc protamine insulin into the same syringe to form a combined dose. It is suggested by some authorities that this technique may result in the soluble insulin being precipitated by excess of zinc and protamine of the zinc protamine suspension, and that therefore the two varieties should be drawn up separately into two syringes when giving a combined dose.

It would appear that zinc protamine mixed with excess of soluble insulin acts as a single compound rather than as a combination of the separate action of the two insulins. Modifications of the standard protamine zinc insulin, containing only half or a third of the amounts of zinc and protamine, have been recommended so as to avoid, if possible, the necessity of supplementary soluble insulin.

Globin Insulin.

This preparation is a compound of insulin with globin, the latter being a protein derived from red cells by abstracting the chromogen fraction. The preparation which contains, also, a trace of zinc chloride is very stable. It is marketed as a clear, yellow solution containing 40 or 80 units per ml. The duration of action is about 18 hours and it is claimed that the doses required are smaller than those of zinc protamine insulin, and that many of the less severe cases of diabetes can be controlled by one injection daily. Globin insulin must never be injected intravenously.

An insulin mixture recently introduced in Denmark is termed Di-insulin. It is a mixture of equal parts of soluble insulin and iso-insulin (phenyl-ureido-insulin). The proportions of the two components are unaltered in the mixture, in contrast to what occurs when the protamine preparations are mixed with soluble insulin. It would appear to be effective as a single injection only in those cases of diabetes requiring less than 50 units daily. This preparation has, so far, not received extensive trials in this country.

Parathyroideum, $\frac{1}{20}$–$\frac{1}{10}$ gr.

Parathyroid substance consists of the dried external parathyroid glands of the ox. Introduced into the blood, parathyroid mobilises calcium, mainly from the bones. It is considered that its initial action is to lower the blood phosphorus level by increased excretion of phosphorus in the urine probably by lowering the renal threshold for phosphates. The blood calcium then rises to ensure that the proportion of calcium and phosphate ions should satisfy the necessary solubility equilibria. The rise in blood calcium is followed by an increased excretion of calcium in the urine. Overdosage with parathyroid results in hypercalcæmia (the serum calcium rising to about 15 mg. per cent.) with symptoms of anorexia, weakness, drowsiness and renal failure. To prevent these symptoms from developing it is desirable to control therapy with parathyroid, by estimations of serum calcium to ensure that this does not rise above 12–13 mg. per cent. Parathyroid therapy is indicated whenever the serum calcium falls to low levels (normal 9–11 mg. per cent.) giving rise to tetany, *e.g.* tetany following operative removal of the parathyroids, also infantile tetany. It has been used successfully as a diuretic in cases of the nephrotic syndrome, although the mechanism of the action here is not at all clear. Parathyroid can be used to eliminate lead from the bones in chronic lead poisoning, since lead is deposited *with* calcium in the bones, and measures employed to mobilise calcium will mobilise lead also. It is not, however, without danger, as a too rapid mobilisation may give rise to acute lead poisoning, and a safer therapy is to give ammonium chloride which, by causing a mild acidosis, leads to a slower mobilisation. The dried gland is given by mouth, but for adequate and rapid medication the hypodermic injection of a suitable preparation must be employed.

Extractum Parathyroidei, B.P.C. (sim. *Parathormone**).
20–40 units by hypodermic injection.

Thyroideum, Off. ½–2 gr. (Off. synonyms: Dry Thyroid, Thyroid Extract, Thyroid Gland).

Normal thyroid gland contains "colloid," which is a globulin with iodine in chemical combination and is termed thyroglobulin. The thyroglobulin complex contains amino-acids with iodine, and the following entities are known to be present: (1) thyroxine, to which the specific calorigenic action of thyroid preparations is mainly due, and (2) di-iodotyrosin, an intermediate product in the formation of thyroxine from tyrosin and calorigenically active only when in combination in thyroglobulin, and not when isolated. Thyroxine and di-iodotyrosin, linked as a peptide, constitute, probably, the true active secretion of the gland.

The official "thyroideum" is intended to provide one standard substance to be dispensed when thyroid gland or "extract" is prescribed. Thyroid is active when given by mouth and, *following a long latent period*, its action is observed as a stimulation of metabolism. The basal metabolic rate is raised from its previous level, the heart is accelerated, in part at least, by direct action on the muscle, and there is increased blood flow through the coronary arteries. Calcium phosphate is mobilised from the bones but, unlike parathyroid action, there is no increase in the serum calcium level. Glycogen is mobilised and hyperglycæmia and glycosuria may occur. This will cause diuresis, and diuresis occurs also as a result of increased protein metabolism leading to urea formation. There is also a considerable withdrawal of water and salts from the fixed tissues into the blood, and the resulting hydræmia in turn provokes diuresis. The loss of fluid is an important factor in the reduction of body-weight following thyroid therapy in myxœdema and obesity. Thyroid is used in medicine to combat the results of deficiency of the natural secretion, notably in cases of cretinism and myxœdema. A remarkable improvement in these conditions follows the stimulation of the depressed metabolism to normality. The treatment of cretins must begin early in life if mental and physical development is to proceed and remain at fairly normal levels. The dosage to achieve this is from 1 to 2 grains daily. In myxœdema it may be necessary to give 3 grains or more daily to keep the disease under control, but it is very important that treatment should begin with a small dosage (say 1 grain daily), otherwise considerable strain is thrown on the heart and dangerous heart failure or *angina pectoris* may follow. Thyroid, used cautiously, is sometimes of value in the lesser degrees of hypothyroidism which women may develop at puberty, and during pregnancy and the menopause, and often associated with obesity, subnormal metabolism, menstrual irregularities and sometimes goitre. In doses of $\frac{1}{10}$ gr. twice daily it stimulates metabolism in marasmus. The diuretic action of thyroid has been used with advantage in cases of the nephrotic syndrome. It may help some cases of psoriasis and other chronic skin diseases. Thyroid extract or thyroxin has been found to increase milk output in cases of failing lactation, as much as 10 gr. daily of the former preparation may be necessary. In these cases there is a deficiency of iodine. Overdosage with thyroid (thyroidism) has already been discussed in part; other effects are tachycardia, fever, headache, sweating, tremor, excitement, excessive loss of weight and diarrhœa. Exophthalmos is rare.

The site of action of the thyroid hormones is undecided. It is suggested that the easier production of thyroidism in myxœdema is due to the collection of a substance in the tissues of untreated cases, because thyroid is not present in sufficient amounts to decompose it as formed. When thyroid is administered in other than small initial dosage, rapid decomposition of this unidentified substance takes place and the products of the decomposition are toxic and give rise to the symptoms described collectively as thyroidism.

Thyroxinsodium, $\frac{1}{640}$–$\frac{1}{64}$ gr.

This is the monosodium derivative of thyroxine; it has the same indications as thyroid and may be given orally or intravenously. If used intravenously, a second injection should not be given until the first has worn off (2–3 weeks). Thyroxinsodium has been used with a special technique for local injection, to improve the blood supply to the ear in cases of otosclerosis.

THE SEX HORMONES

Functions of the Anterior-Pituitary Body.

The sex hormones derived from the anterior lobe of the pituitary are responsible for the normal development of sexual maturity, and functioning of the sexual organs. In the male they stimulate at and after puberty the secretion of the testicular hormone. Similarly in the female, production of the ovarian hormones is mediated, and these act directly on the uterus, regulating the menstrual cycle.

The Anterior Pituitary Gonadotrophic Hormones

The Follicle-stimulating Hormone (*Prolan A**).

(*a*) Stimulates the ovaries and brings about the development of the mature follicle.

(*b*) Ensures the continued secretion of œstradiol into the ripened follicles.

(*c*) Is responsible for the development of the testes, and stimulates the semeniferous tubes.

The Luteinising or Interstitial Cell Stimulating Hormone (*Prolan B**).

This hormone is responsible for the development of *corpora lutea*, which, in addition to œstrogenic hormone, secretes mainly progesterone. In the male the luteinising hormone stimulates the production of testosterone by the interstitial tissues of the testes. Whilst the luteinising hormone is responsible for the actual development of *corpora lutea*, the nutrition and persistence of the latter depend upon another anterior pituitary hormone called the luteotrophic hormone or luteotrophin. It is possible that this may be identical with the lactogenic principle (see below).

These gonadotrophic hormones as well as luteotrophin are also secreted by the human placenta during pregnancy, and their level rises to a peak between the 7th and 9th week. The luteinising hormone in particular is excreted in the urine in large amounts during pregnancy. Certain biological tests for pregnancy depend upon the fact that when the urine of pregnant women is injected into sexually immature female mice (Ascheim-Zondek test) or rabbits (Friedman test), this hormone will result in the formation of hæmorrhagic follicles and *corpora lutea*.

In addition to the above, other recognised anterior-pituitary hormones are:

Thyrotrophic: Controls thyroid activity.

Growth-promoting.

Lactogenic (*Prolactin,* Galactin**): Stimulates and increases the secretion of milk and may be an additional factor in the production of progesterone by the corpus luteum.

Diabetogenic: Is concerned with carbohydrate metabolism and keeps the blood-sugar level high.

Ketogenic: It mediates the metabolism of fats.

Pancreatotrophic: This, apparently, is an entity distinct from the diabetogenic hormone. It stimulates the Islets of Langerhans to produce insulin.

The last three hormones have not been separated, but their presence is suspected from experimental evidence.

Adrenocorticotrophic: Controls adrenal cortex activity.

The anterior-pituitary body has been imaginatively described as the "leader of the hormonal orchestra" and preparations derived from it are used for **stimulation therapy** of the various glands functionally dependent upon its activity. The medicinal use of preparations or isolated principles of these subsidiary glands is described as **substitution therapy.**

Gonadotrophic hormones[1] in therapy are prepared from: (1) **Pituitary gland** (*Ambinon,* Gonadotrophon**). These, whilst theoretically preferable, are difficult to prepare and are not very reliable. (2) **Pregnancy urine,** containing mainly the luteinising hormone, chorionic gonadotrophin (*Pregnyl,* Gonan,* Physostab,* Antuitrin S*), 0·1 mg. = 1 i.u. Chorionic gonadotrophin does not act on the Graffian follicles. (3) **Serum of pregnant mares** (*Serogan,* Gestyl,* Antostab**). Gonadotrophic hormones from this source are probably placental in origin, but they do stimulate the follicles. Commercial preparations are standardised so that 0·25 mg. = 1 i.u. It would appear that the efficacy of serum gonadotrophin is enhanced by the additional administration of chorionic gonadotrophin and that there is probably a synergism between the two. A similar synergistic effect is claimed for a preparation termed *Synapoidin,** in which chorionic gonadotrophin is combined with small amounts of anterior pituitary extract containing the follicle stimulating-hormone.

Therapeutic Indications: Treatment requires the use of injectable preparations given intramuscularly. It is suggested that in the treatment of functional amenorrhœa or hypomenorrhœa due to disturbances in ovarian or pituitary function, therapy should be begun with one of the œstrogens (see below) in the hope of inducing bleeding, and that this should be followed by a course of gonadotrophic hormones. Serum gonadotrophin is given in doses of 200 i.u. and it is combined with urinary gonadotrophin 100 i.u. Injections are given every third day for 15 doses and the course repeated after two weeks. Another method suggested for hypo-ovarianism, resulting either in amenorrhœa or irregular bleeding, and often associated with sterility, is the administration of serum gonadotrophin during the follicular phase of the cycle between the 5th and 14th day, followed by chorionic gonadotrophin from the 15th to the 24th day (luteal phase of the cycle). In the treatment of the more severe types of hypo-ovarianism in which amenorrhœa is associated with uterine hypoplasia and sterility, and in defective spermatogenesis also with sterility, larger doses of serum gonadotrophin, *e.g.* 1,000 i.u. twice weekly, may be given, but improvement, if it occurs at all, is usually transient, as it is generally impossible to give sufficiently large doses to effect anatomical improvement in the underdeveloped organs. *Synapoidin** is given in doses of 1–2 ml. three times weekly. Urinary gonadotrophin is of value in the treatment of undescended testes, the dose used being 500 i.u. twice weekly if the testes are in the abdomen, and once weekly if they are in the inguinal canal. Treatment should not be begun before the age of seven or after thirteen. It may also be of value in metropathia hæmorrhagica by depressing follicular activity. Urinary gonadotrophin is used, with doubtful value, in recurrent abortion. The growth hormone (*Antuitrin G*) is sometimes prescribed in pituitary infantilism, as are preparations from mares' serum.

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[1] These hormones have not yet been isolated in the pure state.

Injectio Gonadotrophini Serici (*Serogan**), 200–1000 units. Serum gonadotrophin is supplied in solid form in sealed ampoules. Solution in sterile water containing 0·5% phenol is effected immediately prior to injection.

Lactogenic hormone (0·1 mg. = 1 i.u.) is given to stimulate and increase lactation. A commonly used preparation is *Physolactin** in doses of 5, 5, 2, 2, 1, 1 mls. subcutaneously on successive days.

Testicular and Ovarian Hormones

It is to be emphasised that sharp demarcation of function does not exist between the hormones of the testes and of the ovaries. They are all sterols, *i.e.* relatively simple derivatives of a saturated hydrocarbon—cyclopentenophenanthrene—and in view of their close chemical relationship it is hardly surprising that nearly all are ambisexual to a greater or less degree.

The cortical hormone, corticosterone, is very similar in chemical constitution to these substances, and it is thought that the suprarenal cortex may secrete a precursor which is subsequently modified by the ovaries and the testes in fabricating their respective secretions. Broadly the functions of these substances are as follows:

Androgens (male hormones). Testosterone and its derivatives.

Testosterone is the true testicular hormone, which can be isolated from the testes of bulls or prepared from the appropriate sterol. Androsterone is the hormone present in the urine and is derived from testosterone. The actions of the androgens are as follows:

(*a*) Bring precocious maturity to immature animals, where their injection produces the development of the accessory reproductive organs. Therapeutically they are given to cases of arrested puberty, due primarily to testicular hypoplasia or absence, such as eunuchoidism, hypogonadism and cryptorchidism. They have no direct effect on the testes, but only on the accessory sex organs. Care must be taken to avoid too high a dosage in youths who are physically and psychologically unprepared for full sexual maturity. In undescended testes, therapy should only be undertaken if there is no response to gonadotrophin. Testosterone has been found of value in cases of refractory hypochromic anæmia associated with hypogonadism.

(*b*) Prevent onset of castration changes, and are therefore of value after surgical castration.

(*c*) In adult males they have been employed to correct functional deficiency at the male climacteric, in cases of impotence and in the effeminate type, and also in Cushing's syndrome and Addison's disease.

(*d*) In cases of deficient testicular function, such as early senility, they may exert a restorative effect on metabolism and the physical and mental tone generally, probably as an indirect effect of the hormones. Libido may be stimulated, but not spermatogenesis. They are, however, dangerous in the presence of hypertension.

(*e*) They are used, but with indefinite clinical results, in the early stages of benign prostatic enlargement, a condition thought to be due to œstrogen/androgen imbalance.

(*f*) In the female they may be androgenic, *i.e.* masculinising, or gynæcogenic, *i.e.* feminising, promoting the development of the infant uterus. In large doses they reduce the activity of the anterior pituitary gland and so inhibit ovulation and menstruation and also affect the activity of the breasts. They may cause masculinising symptoms. In doses of 100 mg. per 10 days they are given in the treatment of menorrhagia, metrorrhagia and chronic mastitis. It is claimed that testosterone propionate (*q.v.*), 100 mg. three times weekly, will relieve pain due to bone metastases of mammary cancer.

(*g*) They produce growth of the capon's comb, and this fact has been utilised in the biological assay of the substance (0·1 mg. crystalline androsterone = 1 i.u.). In adrenal cortical tumours, the excretion of androgens in the urine is high both by biological and colorimetric assays.

They are contraindicated, or of no value, in sterility, carcinoma of the prostate, or in hypopituitarism unless there is undescended testes. They may effect temporary improvement in *angina pectoris*. They may cause azoospermia if given to patients with normal testes. Other toxic effects are heart failure, œdema and hypermetabolism.

Œstrogens (female hormones). Œstradiol (a dihydric alcohol) and its derivatives:

(*a*) As they are responsible for the earlier proliferative endometrical changes of the menstrual cycle, they are necessary for normal œstrus in animals and menstruation in humans. When administered to immature females and castrates, they will evoke œstrus by bringing about the necessary endometrial changes.

(*b*) They are responsible for the normal development of the uterus and mammary glands, particularly of the ducts and nipples, and the secondary sexual characteristics. When administered to immature animals this development is prematurely induced, and when given to castrates they will prevent atrophy of the uterus and mammary glands and loss of the secondary sexual characteristics. They are responsible for contractility of the uterus and its sensitivity to oxytocin, and thus help to initiate labour.

(*c*) Antagonise the gonadotrophic pituitary hormones. This results in reduced ovarian stimulation, an important factor in the alternate phases of activity and quiescence of the menstrual cycle, and leads to proper functional co-ordination between the anterior pituitary and the ovaries. Testosterone acts similarly in relation to the testes and the anterior pituitary. Injections into animals of œstrogens or of testosterone can cause atrophy of testes and ovaries with infantilism as a result of their inhibitory action on the anterior pituitary. Œstrogens also inhibit the lactogenic principle, although œstrogen deficiency may prevent satisfactory lactation from being established in the first few days of the puerperium.

(*d*) Large doses in male animals may cause prostatic enlargement with urinary retention.

(*e*) They produce cancer of the breast in mice. This is of no clinical significance.

(*f*) The œstrogen secreted by the ovaries is œstradiol, and this is converted into, and excreted in the urine as, œstrone and œstriol glycuronides. The conversion of œstrone into œstriol may depend on progesterone, and it has been suggested that when progesterone is deficient, accumulation of œstrone may result in menstruation or labour. α-œstradiol is active and β-œstradiol is inactive. Œstrone is more active than œstriol. During pregnancy, as a result of placental secretion, there is a rise of œstrogens in the urine from the second month to term. When injected, œstrogens are largely destroyed by the liver.

(*g*) Natural œstrogens are very much more effective by injection than by mouth. Their action is prolonged by injecting intramuscularly a suspension in oil or implanting in solid crystal form. Activity is prolonged by using esters such as the benzoate or propionate.

(*h*) Synthetic œstrogens like stilbœstrol and hexœstrol are bactericidal and bacteriostatic to certain organisms. The natural œstrogens have no such action.

The actions mentioned above suggest the value of œstrogen therapy in disorders of the climacteric. Beneficial results from such administration at the menopause have been summarised (Levy Simpson, 1938) as follows : œstrogens—

(i) Abolish vasomotor symptoms, especially " hot flushes."
(ii) Decrease general nervous irritability and anxiety, including involutional melancholia.
(iii) Frequently ameliorate or abolish migraine.
(iv) Improve or cure *pruritus* and *kraurosis vulvæ*, *leucoplakia vulvæ*, senile vaginitis, etc.
(v) Decrease hypertension.
(vi) Improve carbohydrate tolerance.

If œstrogens are administered at the first sign of climacteric disturbance, and the administration is continued for a prolonged period with very gradual withdrawal, the mental and physical strain usually associated with this period may be largely overcome. Vasomotor disturbances, headaches, formication, insomnia, irritability, etc., are greatly ameliorated. Migraine, whether associated with the menopause or not, and in both sexes, may occasionally be successfully treated by a course of injections of œstradiol benzoate in large doses. The mechanism of this is possibly an antagonising action on the gonadotrophic hormones which, in migraine, are thought to be excreted in excess. Chronic arthritis due to the menopause and hypo-ovarianism may be ameliorated. One scheme of dosage which may be employed at the menopause is œstradiol benzoate 100,000 i.b.u. weekly for two weeks followed by 20,000 i.b.u. weekly. Alternatively, 0·5–1 mg.

stilbœstrol daily may be prescribed. Œstrogens may cause post-menopausal metrorrhagia if given in unnecessarily large doses over a long period. At the menopause they should only be used for symptoms which can definitely be attributed to the climacteric. The local application of œstrin dissolved in olive oil has proved, clinically, to be a most useful treatment for atrophic rhinitis in both sexes.

Both in simple leucorrhœa and the gonococcal vulvo-vaginitis of children, œstradiol (1,000 units) yields excellent results whether applied locally, in the form of vaginal suppository for example, or given by intramuscular injection. Alternatively, stilbœstrol 0·5 mg. daily up to 1 year and 1–3 mg. daily up to 10 years can be administered, or hexœstrol given in four times this dosage. In the former case, the hormone promotes premature epithelialisation, renders the secretion acid and encourages the appearance of a normal vaginal flora. Other uses of œstrogen therapy are the alleviation of artificial menopause after ovarectomy or deep X-ray therapy to the ovaries, and the treatment of recent secondary amenorrhœa either alone or followed by progesterone. Kaufmann recommends for ovariectomised women ½–1 million units of one of the natural œstrogens, followed by 100 units of progesterone over a period of three weeks. Primary amenorrhœa over the age of twenty is rarely benefited by this treatment, but the treatment may benefit cases of delayed puberty with primary amenorrhœa or scanty menstruation by stimulating growth of the hypoplastic uterus, but such improvement can only occur when the hypoplasia is not pronounced (see also gonadotrophin). Œstrogen therapy will also stimulate uterine tone in uterine inertia or abortion. Œstradiol benzoate 250,000 i.b.u. spread over five weeks is a suitable dose for uterine hypoplasia. Œstrogenic hormone is also of considerable value in inhibiting the secretion of milk in the puerperium when it is necessary to wean the infant. Stilbœstrol 5–15 mg. is a suitable dose for this purpose, and this can be followed by two further doses of 5 mg. given on consecutive days. Given in doses of 5 mg. thrice daily for 4 days before the period, stilbœstrol may be of value in dysmenorrhœa in which the pain comes on at the onset of the menstrual flow. Œstrogens have also been given in conditions of peripheral vasospasm, such as Raynaud's disease, as it is thought that they cause acetylcholine to be liberated locally.

Progesteronum (Progestin).

Progesterone is the hormone of the *corpus luteum.* During pregnancy after the third month it is also secreted by the placenta. It is excreted into the urine during the *corpus luteum* phase of the menstrual cycle and during pregnancy as the inactive pregnanediol glycuronide, the excretion increasing towards parturition. Modifications of progesterone such as ethisterone are active by mouth, unlike progesterone itself. Progesterone gives rise to the later endometrial changes in the menstrual cycle. These comprise a transformation from the proliferative to a secretory phase. The endometrium then becomes suitable for reception of a fertilised ovum. If fertilisation of the ovum does not occur, the *corpus luteum* regresses, the secretion of progesterone is reduced and menstruation occurs. Progesterone is important for the development of the placenta and nutrition of the embryo. It maintains pregnancy, probably by diminishing the uterine sensitivity to the motoric effect of oxytocin. During pregnancy it inhibits ovulation. It also assists œstrogen in the development of the mammary glands. The chief indications of progesterone are: inadequate *corpus luteum* formation, the regularisation of menstruation, and in certain cases of recurrent and threatened abortion.[1] In habitual abortion it can be given for two months commencing one month before the usual time of abortion, either 1–5 mg. daily by injection or preferably as ethisterone 10–60 mg. daily by mouth. It is an advantage to combine such treatment with vitamin E. In threatened abortion, it is injected in doses of 5–10 mg. daily during the critical phase. It is useful in dysmenorrhœa by reducing uterine motility, and in menorrhagia, particularly in *metropathia hæmorrhagica*, by suppressing the menstrual flow. In the latter condition there is a disturbed rhythm between follicular and corpus luteum activity, the abnormal bleeding being due to deficient progesterone production resulting in the unchecked activity of œstrogenic hormones. A suitable dose is 5 mg. daily for six days. Recent American work suggests that progesterone, in common with other 3-keto-steroids such as desoxycorticosterone and testosterone, can prevent fibroids in guinea-pigs from being produced by œstrogens. Progesterone in doses of 10 mg. 3 to 6 times weekly can cause regression of uterine fibroids in women.

Sources and Dosage of the Products used Clinically

The therapeutic indications of the following preparations have been given in the preceding sections which should be consulted. Further indications are mentioned only if not already given.

Testosterone.

This is prepared from bulls' testes or synthesised from cholestrol. Testosterone propionate 5–25 mg. daily or 3 times a week by injection or inunction is the most active androgen preparation and is most commonly given. Subcutaneous implantation of tablets (300–1,600 mg.) exert a prolonged action but are more uncertain. Methyltestosterone 25–100 mg. daily is effective by mouth and has a more prolonged action. Sublingual absorption is effective. A maintenance dose should be determined for each case. Priapism indicates excessive dosage.

Androsterone.

This is an excretion product of testosterone and is obtained from male or female urine or synthesised from cholestrol. Dose: 5–25 mg. daily or 3 times a week. An oily preparation is used.

Œstradiol (*Dihydrotheelin**). Dose: 0·1–0·2 mg. (5,000 to 10,000 i.u.) daily by mouth.

This is the true follicular hormone, but it is produced in small quantities in the testis. It is obtained from ovarian tissue or pregnancy urine. Crystals of œstradiol 75 mg. can be implanted subcutaneously and are effective over a long period.

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[1] Recent evidence suggests that progesterone is only of value in threatened abortion if there is actual deficiency of the hormone (as determined by pregnanediol excretion in the urine), otherwise its administration may do harm.

Œstradiol Benzoate.

Dissolved in oil is administered by intramuscular injection in a daily dosage of 1–5 mg. (10,000 to 50,000 i.u.).

Œstroradiol Dipropionate.

This can be given intramuscularly in doses of 0·5–1 mg. 3 times weekly for 8 weeks in the treatment of vasomotor disorders (see above).

Œstriol (*Theelol**).

Is an alcohol obtained from placental tissue and pregnancy urine. It is administered orally. Dose: 0·05–0·5 mg. (500 to 5,000 i.u.) daily.

Œstrone (*Theelin**).

This ketone is an excretion product of œstradiol and is separated from male or female urine. It is given orally, dosage 0·1–5 mg. (1,000 to 50,000 i.u.), or by intramuscular injection of an oily solution 0·5–1 mg.

Œstrone Benzoate.

Is produced by the esterification of the phenolic group in œstrone. It is administered intramuscularly in oily solution, dosage 1–5 mg. (10,000 to 50,000 i.u.).

Dienœstrol.

This substance is a synthetic œstrogen which is effective by mouth. The physiological effects and therapeutic indications are the same as for stilbœstrol, 0·3 mg. of dienœstrol is approximately equivalent in its effects to 1 mg. stilbœstrol, and the dosage should be correspondingly less. It is free from the toxic effects, such as nausea and vomiting, sometimes induced by stilbœstrol, unless used in massive doses.

Hexœstrol. Dose: 0·001–0·005 gm. ($\frac{1}{60}$–$\frac{1}{12}$ gr.).

This œstrogen is obtained by the hydrogenation of stilbœstrol or from anethole. It can be given by mouth or by injection like stilbœstrol and is said to be less toxic than the latter. Orally it is less liable than stilbœstrol to give rise to nausea. **Hexœstrol dipropionate** in oil is given by intramuscular injection.

Progesterone (Progestin).

Progesterone is extracted from lutein tissue or prepared artificially from stigmasterol, a sterol found in the soya bean. It has been administered by mouth, but the only satisfactory route is intramuscular injection of an oily solution, although implantation of 100 mg. pellets may be effective. Dose: 0·001–0·01 gm. Anhydro-oxyprogesterone (**ethisterone,** formerly called pregneninolone) 10–60 mg. daily has the great advantage of being effective by mouth.

Stilbœstrol (Diethyl-Stilbœstrol). Dose: 1–5 mg.

Stilbœstrol is a derivative of anethole, it has the same physiological action as ovarian follicular hormone with the added advantage of complete effectiveness when taken by mouth. One milligram of stilbœstrol administered orally is equivalent in effect to 0·5 mg. of œstradiol benzoate by injection. Treatment with stilbœstrol is usually initiated by a dose of

0·001–0·002 gm. ($\frac{1}{60}$–$\frac{1}{30}$ gr.) 3 times a day, and this is shaded off to the minimal maintenance dosage. Crystals of 100 mg. can be implanted subcutaneously and provide prolonged medication. Recently stilbœstrol has been shown to effect a remarkable remission of the symptoms in cases of neoplasm of the prostate and metastases therefrom with a fall in the level of the serum acid phosphotase. Claims have been made that the drug has some palliative value in the treatment of the osseous metastases of breast carcinoma, especially in the aged. The dose recommended for prostatic cancer is 1 mg. 3 times weekly, increasing if necessary to 15 mg. daily until symptoms abate. This should be followed by a maintenance dose of 1–2 mg. daily. Œstrogen therapy is of no benefit in benign prostate enlargement and, indeed, may be detrimental in these cases. The drug may cause vertigo, nausea, vomiting and skin eruptions. In males it may result in testicular shrinkage with loss of libido.

Stilbœstrol Dipropionate. Dose: 0·001–0·005 gm. ($\frac{1}{60}$–$\frac{1}{12}$ gr.).

This ester is administered orally or by the intramuscular injection of an oily solution. Its action is milder but more prolonged than that of stilbœstrol, and its principal use is for injection where stilbœstrol by mouth produces nausea.

Triphenylchlorethylene (*Gynosone**).

This is a synthetic substance with an action similar to that of the natural œstrogens. It has the same therapeutic indications as other œstrogenic substances and is effective by mouth, parenterally and by local application. Orally its duration of action is about the same as that produced by stilbœstrol, but when injected parenterally its effect is much more prolonged.

Dosage.—Oral: The drug is prepared in tablet form, each tablet containing 250 mg.; as many as nine of these may be given daily. By injection: 250 mg. at intervals of 1–4 weeks. Vaginal suppositories, each containing 100 mg., may be inserted nightly.

D.B.E. *aa* di-(*p*-ethoxyphenyl)-*β*-phenyl bromoethylene.

This is a recently introduced synthetic pro-œstrogen. Given orally it is absorbed from the intestinal tract. Although it has a more prolonged action than the other orally active œstrogens, it is less potent. It is stored in the fatty tissues, is excreted slowly and has low toxicity. A loading dose of 1–2 gm., followed by a maintenance dose of 0·1–0·3 gm. weekly, is used in the treatment of the menopause. It is of less value in uterine atrophy and of no use in prostatic carcinoma.

ANTI-THYROTOXIC DRUGS

The following drugs are used in the treatment of thyrotoxicosis:—

Thiouracil and Methyl Thiouracil.

Thiouracil is 2-thio-6-oxypyrimidine. These drugs belong to a series of thiol compounds containing the grouping >N-CS-N< which are capable of reducing the activity of the thyroid gland and are therefore of value in the medical treatment of hyperthyroidism. Although thiourea was the original compound used, the thiouracil group is less toxic and has replaced the former. They act not by neutralising thyroxine but by preventing the accumulation of iodine and the synthesis of thyroxine. This they do by inhibiting the union of iodine and tyrosin into di-iodotyrosin, the precursor of thyroxine. It is possible that these compounds inhibit the action of an enzyme responsible for the liberation of iodine from iodide. Their affinity for iodine may also be a factor in preventing the synthesis of thyroxine. When employing these drugs in the treatment of thyrotoxicosis, a time-lag of one or two weeks is observed before there is relief of symptoms, and maximal improvement is generally noticed after about a month. On the whole, control of the disease is more rapidly obtained with methyl thiouracil. Recent treatment with iodine delays the response to thiouracil therapy as the precursors of thyroxine compete with thiouracil for the greater quantity of iodine available. Some symptoms, such as restlessness and sweating, tend to be more rapidly relieved than others, such as tachycardia. There is a fall in the B.M.R., gain in weight, rise in the blood cholestrol and, frequently, restoration of normal cardiac rhythm in patients with auricular fibrillation. Where the disease is of recent onset, eyelid retraction but not proptosis is reduced. These drugs may cause hyperplasia and enlargement of the thyroid gland if given in excessive doses. This is brought about by the thyrotropic hormone of the pituitary as a compensatory mechanism for inadequate thyroxine production. A goitre persists in most of the patients treated with these drugs. Although these drugs, by reducing hyperthyroidism, are of value before thyroidectomy, they have the disadvantage of acting more slowly than iodine therapy and of adding to the technical difficulties of the operation by increasing the size and vascularity of the gland, although bleeding at the operation can be reduced by giving a pre-operative course of iodine. A common practice for patients who are to undergo thyroidectomy is to get the patient under control with thiouracil and then to give a pre-operative course of iodine.

Toxic Effects: Granulocytopenia may occur and agranulocytosis is an uncommon but occasional fatal complication. It occurs most frequently between the 4th and 8th weeks of treatment. Blood counts, particularly in the presence of fever or sore throats, and the avoidance of overdosage are important measures for reducing the incidence of agranulocytosis. Other complications described are drug fever (most usual about the 10th day), toxic dermatitis with maculo-papular and urticarial rashes, petechiæ, enlarged lymph glands and spleen, joint effusions, conjunctivitis, jaundice, heart block, pulmonary œdema and *periarteritis nodosa*. Gastric upset and halitosis occurs with thiourea. Myxœdema may occur occasionally, but is temporary and disappears when the dosage is reduced.

Dosage: These drugs are administered orally. An initial test dose of 0·1 gm. is given and, if no reaction follows, 0·2 gm. or 0·3 gm. is given daily in divided doses of 0·1 gm. until the B.M.R. is about normal and there is definite gain in weight. A maintenance dose, which should be the lowest to keep the patient well, is then continued, and may vary from 0·25 gm.–0·1 gm. daily. Such maintenance therapy needs generally to be kept up for many months or even years, otherwise relapse may follow. The drug need not be discontinued if there is drug fever, unless agranulocytosis also develops. Agranulocytosis should be treated with pyridoxin and penicillin.

Whilst many cases of thyrotoxicosis can be brought under satisfactory control with these drugs without resort to thyroidectomy, there is the disadvantage that a prolonged course of therapy is necessary. The drugs are useful in severe operative risks and the mortality from them is, as a rule, less than from operation, whilst, apart from the danger of agranulocytosis, complications are less serious. On the other hand, operation should be carried out in patients who have large nodular goitres, tracheal compression, drug reactions, or who cannot attend regularly for supervision. Some physicians prefer to discontinue the drug during pregnancy because of animal experimental evidence that the drug injures the fœtus, although there is little clinical experience to support this.

Methyl thiouracil is claimed to be less toxic and to act more rapidly than thiouracil and to be less likely to cause thyroid hyperplasia.

Propyl thiouracil is about four times as potent as the methyl compound and can be used in smaller doses, 150 mg. daily being given until control is established, followed by a maintenance dose of 25–50 mg. daily. Recent evidence suggests that the effective dosage is higher than this and approximates to that of the other thiouracil compounds. It is much less prone to produce serious complications, such as agranulocytosis.

Recent work suggests the possibility of employing these drugs as an alternative to thyroidectomy in cases of chronic congestive heart failure and *angina pectoris* not responding to other measures.

For antithyrotoxic action of **iodine** and **iodides,** see Index.

Di-iodotyrosin in doses of 100 mg. has been used in the treatment of hyperthyroidism.

OILS, FATS AND WAXES

THE volatile oils are considered elsewhere: this section deals only with the so-called fixed oils. Fixed oils may be hydrocarbons which are of mineral origin (*e.g.* liquid paraffin or petrolatum) or they may consist, in the main, of the glyceryl esters of higher fatty acids (oleic, palmitic, stearic, etc.), and these are derived from organic sources. With certain specific exceptions (*e.g.* castor oil) these animal or vegetable oils are digested and absorbed, and constitute fuel foods. They may be saponified with aqueous alkali, with the liberation of glycerin and the formation of soaps. Fats or "butters" of animal and vegetable origin are related in composition to the oils, and indeed the terms "oil" and "fat" are purely arbitrary, since the same substance may be liquid or semi-solid according to the ambient temperature. Mineral fat (soft paraffin, sim. *Vaseline**) consists of hydrocarbons only. Hard paraffin (paraffin wax) consists of high boiling-point hydrocarbons. True waxes are of organic origin; they consist of higher fatty acids combined with alcohols other than glycerol; examples are wool-fat and beeswax. Applied to the skin, the mineral products exert only a superficial action, while those of animal or vegetable origin are absorbed to some extent, and promote the absorption of medicaments which may be compounded with them.

Adeps (Lard).

Lard is the purified internal fat of the pig. It is used as an ointment base, but as it is liable to rancidity, benzoinated lard is preferred except for eye ointments, where it would be too irritating. As an ointment base, lard is now largely replaced by the official Simple Ointment.

Adeps Benzoinatus, Off.

Benzoinated lard contains the antiseptic, fat-soluble esters and acids from benzoin.

Cera Alba (White Beeswax).

Cera Flava (Yellow Beeswax).

The waxes are used to stiffen ointment bases and to make "water-in-oil" emulsions.

Adeps Lanæ.

Wool-fat is a mixture of waxes together with cholesterol and *iso*-cholesterol. It is obtained from sheep's wool, and closely resembles the fatty secretion of the human skin. When admixed with soft paraffin to form an ointment base, it promotes the absorption of medicaments which may be incorporated in the ointment. Like beeswax, wool-fat may be used to prepare "water-in-oil" emulsions.

Adeps Lanæ Hydrosus, Off. (Lanolin).

Lanolin is largely used in conjunction with soft paraffin, as a skin emollient and as a base for ointments containing medicaments which are intended to pass through the skin.

Oleum Amygdalæ.

Almond oil is an emollient, and internally a nutriment. It is applied to the hair where the scalp is deficient in natural secretion. Almond oil has little odour and is less liable to rancidity than other vegetable oils in common use.

Oleum Arachis (Pea-nut Oil).

Arachis oil is a bland nutritive oil which is often used to replace olive oil for all purposes.

Oleum Hippoglossi (*q.v.*).

Oleum Lini.

Linseed oil is not generally used internally, but is widely employed in the arts. It was a component of " Carron Oil," a preparation formerly applied as a dressing for burns, which consists of equal parts of linseed oil and lime water, shaken together to form an emulsion containing an aqueous internal phase.

Oleum Morrhuæ (*q.v.*).

Sodii Morrhuas (Sodium Morrhuate).

The sodium salts of the unsaturated fatty acids of cod-liver oil have been used of 3% solution subcutaneously in the treatment of leprosy. Solutions containing 5% and 10% are used for sclerosing in the injection treatment of varicose veins, hæmorrhoids and varicocele, but they are liable to give rise to anaphylactoid reactions, and some clinicians prefer to use solutions of ethanolamine oleate on this account. Sodium morrhuate is sometimes injected into the pleural cavity in cases of recurrent spontaneous pneumothorax to promote fibrin formation in order to seal the leak. Other substances which have been used for this purpose are Gomenol, silver nitrate and sterile talc powder containing 2% of iodine.

Ethanolamine Oleate (*Ethamolin**).

An aqueous 5% solution of this compound with 2% benzyl alcohol is used for the sclerosis of varicose veins. The dose injected into the affected veins varies from 0·5–2 ml. Contraindications to such therapy are thrombosis of deep veins, marked œdema, heart or renal impairment, diabetes, thyrotoxicosis, pregnancy, varicose eczema or ulceration.

Injectio Æthanolaminæ Oleatis, Off. 30 to 75 min.

Oleum Olivæ, ¼–1 fl. oz. (Salad Oil).

Olive oil is a bland vegetable oil largely used as a nutriment, laxative and emollient. Taken by mouth it is partly split by the stomach lipase and partly emulsified by the emulgent properties of other foodstuffs and by traces of bile in the stomach. In the small intestine, emulsification proceeds further under the influence of the bile salts, and hydrolysis is continued by the pancreatic lipase. The products of hydrolysis are glycerin and oleic acid, and the latter combines with intestinal alkali to form a soap. The products of these digestive processes are therefore water-soluble and they are absorbed. In the intestinal wall, however, reconstitution of the oil takes place and reconstituted oil globules are found in the lacteals; whence they reach the blood-stream *via* the thoracic duct. In larger dosage some of the oil escapes digestion and acts as a laxative. "Stones" of calcium soap may be formed in the intestine; these are sometimes mistaken by patients for gall-stones.

Olive oil is given before food in cases of hyperchlorhydria since oils and fats tend to diminish the flow of gastric juice. This inhibitory action appears to be independent of the local nerve connections, and one theory is that it stimulates the production of an intestinal hormone, enterogastrone, which has an inhibitory action on the gastric secretion. Warm oil may be placed in the ears to soften hard wax, and injected rectally to assist the passage of impacted fæces. Since oils and fats cause biliary flow by reflex from the duodenum, olive oil is used sometimes in the treatment of cholecystitis. It is applied externally as an emollient. The oil is largely used as a vehicle for oil-soluble substances such as sulphur and camphor, which are intended for intramuscular injection, and insoluble salts such as bismuth salicylate are suspended in the oil for depot therapy. For parenteral purposes olive oil is sterilised by heating at 150° C. for one hour.

Paraffinum Durum.

Hard paraffin, sometimes wrongly called paraffin wax, is a hydrocarbon obtained from the high boiling-point fractions of petroleum distillation. It is used to stiffen ointment bases, and injections of paraffin wax have been used to shape features in plastic surgery. So used, however, it may give rise to chronic irritation with the eventual production of paraffinomata.

Paraffinum Liquidum (*q.v.*).

Paraffinum Molle Album (White *Vaseline** sim.).

This is prepared by bleaching yellow soft paraffin.

Paraffinum Molle Flavum (*Vaseline,** sim.).

Yellow soft paraffin is a hydrocarbon product of petroleum distillation. It enters largely into the composition of ointment bases because of its bland, non-reactive character. For many lubricating purposes it is too stiff, and a mixture of equal weights of soft and liquid paraffins, prepared by fusion, is more acceptable.

*Tulle Gras** Dressing (*Nonad Tulle,** *Optule,** sim.).

This proprietary surgical dressing consists of a wide-mesh gauze fabric impregnated with soft paraffin containing a little balsam of Peru and olive oil. The whole is sterilised by heating in a sealed container at 150° C. for one hour. It is used as a protective and to stimulate healing in extensive burns and for skin grafts. Various modifications of the original formula are in use, particularly those made with cod-liver or halibut-liver oil in place of the olive oil. A very useful addition is 0·1% of *Nupercaine** base, the anæsthetic properties of which contribute considerably to the comfort of the patient.

Unguentum Simplex, Off.

This comprises an admixture of hard and soft paraffins with wool-fat, and is a useful ointment base for most purposes.

Unguentum Alcoholicum Lanæ (*Eucerin**).

This is an elegant base for dermatological preparations, and as an emollient. It contains 50% of water dispersed in a fatty medium.

SUGARS, STARCHES AND GUMS

Acacia (Gum Arabic).

Acacia possesses the property of forming a mucilage with water. It is used largely to disperse insoluble powders or precipitates in mixtures, and to prepare emulsions of oils with an aqueous external phase. As a colloid it may be injected with sodium-chloride solution intravenously in the hope of retarding the elimination of the salt and of water, but the clinical evidence appears to show that the retarding effect is not pronounced.

Injectio Sodii Chloridi et Acaciæ, B.P.C. (Gum-Saline).

Mucilago Acaciæ, Off. (Mucilage of Acacia).

This is added to mixtures in the proportion of about 1 fl. dr. to 1 fl. oz. of mixture to disperse precipitates.

Amylum.

Starch is a polysaccharide, insoluble in water, but swelling with boiling water to a translucent jelly. It is digested in the small intestine provided that it has undergone preliminary treatment (cooking) to rupture the starch grains, and converted into dextrose which is absorbed. Starch is applied externally for its absorptive and protective properties; it is usually admixed with a proportion of zinc oxide, boric acid, talc and sometimes light magnesium carbonate to neutralise acid sweat. A thin mucilage of starch may be used as a vehicle for the rectal injection of chloral hydrate or paraldehyde to reduce local irritation by these drugs. Special starches, such as arrowroot, are administered as a well-boiled, thin mucilage, sometimes sweetened, to act as demulcents to the intestine in cases of enteritis.

Dextrosum, Off.

Dextrose is a soluble monosaccharide which is administered by mouth or by intravenous injection, a 5% solution is isotonic with blood. Both subcutaneous and rectal injection are practised also, but the former is undesirable because of the risk of infection, while absorption from the rectum has been shown, recently, to be poor. Dextrose is of a high standard of purity suitable for intravenous injection ; for other purposes a commercial variety known as "powdered glucose," or else liquid glucose, may be utilised. Intravenous dextrose therapy is useful:

1. In cases of shock due to trauma, operations, etc.
2. With insulin in diabetic coma. Here the dextrose is added to prevent dangerous hypoglycæmia following the action of the insulin and to ensure the disappearance of ketone bodies during combustion of the dextrose. It is, however, better omitted in the early stages of treatment of diabetic coma.
3. In severe acidotic states with much vomiting, *e.g.* cyclical vomiting. In these cases there is need for the dextrose as a nutriment and to counteract ketosis, but even more need for the introduction of fluids, and the condition can best be treated by drip infusion of 5% dextrose in saline or one of the alternative solutions referred to in the monograph on sodium chloride.

In the following conditions the intravenous injection of a strong solution (*e.g.* 50%) is of value in:

1. Hypoglycæmic coma.
2. Anuria; 200 ml. exert a powerful diuretic effect during excretion of the sugar by the kidneys.
3. Increased intracranial pressure, *e.g.* cerebral tumour, cerebral trauma and hypertensive encephalopathy. In these conditions 100–200 ml. are given, and acts by virtue of the osmotic effect withdrawing water from the œdematous brain through the choroid plexus.

By mouth, dextrose is a fuel food which, in exceptional conditions, may be of special value because it needs no digestion before it can be absorbed, but in the vast majority of cases sucrose (*q.v.*) is equally effective and very much cheaper.

On account of its aldehyde structure, dextrose reduces Fehling's solution and is sometimes added to preparations of ferrous iron to retard oxidation.

Injectio Dextrosi, Off.

A sterile solution containing 5% of dextrose.

Galactosum.

Galactose is a monosaccharide produced, together with dextrose, by the hydrolysis of lactose. It is used as a test of hepatic efficiency; 40 grammes in 400 ml. of water are administered to the fasting patient and five or six samples of venous blood are taken at thirty-minute intervals. There is no pronounced rise in the blood-sugar curve unless the liver cells are too grossly damaged for the normal glycogenic function of the gland to be performed adequately.

Lactosum.

Lactose is a disaccharide present in mammalian milk. It has an aperient action on infants comparable with that of sucrose. It is used sometimes as a vehicle for the administration of calomel, etc., in powder form. Lactose is given concurrently with cultures of *Bacterium acidophilus* to encourage proliferation of these bacteria in the treatment of intestinal disorders.

Sucrosum (*Saccharum Album*).

Cane sugar is a disaccharide largely used as a sweetening agent. It tends to exert an aperient effect on young infants, who are usually unable to hydrolyse more than a very limited quantity. The unsplit sugar, like all disaccharides, cannot be absorbed and it irritates the intestinal mucosa. A concentrated solution (*Syrupus*, Off.) exerts a high osmotic pressure and so inhibits the growth of moulds, etc.; it is used, therefore, as a preservative vehicle for medicated syrups. On hydrolysis, sucrose is converted into equal molecules of dextrose and lævulose. Intravenously, sucrose may be injected as a diuretic and for cerebral œdema in the same way as dextrose and in similar concentration. When so injected, sucrose, as a non-threshold substance, is even more effective than dextrose as a diuretic, and its action in cases of cerebral œdema is more prolonged. Orally, in addition to its value as a food, it will relieve hypoglycæmic attacks.

Pectin (*Aploma,* Nipectin**).

This is a complex carbohydrate used in the manufacture of jams and jellies. It is used orally in the treatment of infantile enteritis, and its presence in apples is the basis of the "raw apple" treatment for the same condition. It probably acts by the absorption of toxins. Apple pectin experimentally inhibits the growth of influenza virus.

Ivax.*

This is a liquid extract of apples used in the treatment of infantile enteritis, colitis and dysentery. Each fluid ounce is equivalent to 4 ounces of fresh apples. The dosage is 2–3 ounces daily for infants under 1 year, and ½–1 ounce every 2 hours for children over 1 year and for adults. The therapeutic effects are probably due to the pectin content.

Saccharinum, Off.

Apart from its use as a sweetening agent, saccharine is sometimes injected intravenously in doses of 2 gm. in the estimation of the "arm to tongue" circulation rate.

*Sorbitol** is an alcohol obtained from pears and apples. It is used as a substitute for glycerin and as a sweetening agent in diabetes since it does not raise the blood sugar.

Tragacantha.

Gum tragacanth slowly swells with water to form a mucilage. This may be added as a suspending agent to mixtures containing constituents with which acacia is incompatible. Viscous gels made with tragacanth, and usually a proportion of glycerin, are largely used as a water-soluble vehicle for medicaments for local application, where the greasiness of a normal ointment base may be undesired. Tragacanth lacks the emulgent properties of acacia, but is sometimes added to increase the viscosity of emulsions. In very fine powder tragacanth is used to dust over loose dental plates to make them adhere to the roof of the mouth.

Pulvis Tragacanthæ Compositus, Off.

This is added to mixtures as a dispersing and suspending agent.

PROTEINS AND AMINO-ACIDS

In certain conditions where there is gross impairment in the powers of ingestion, digestion or absorption of food it has been found possible to maintain adequate nutrition by the oral or intravenous administration of solutions containing amino-acids, dextrose and sodium chloride. The administration of amino-acids aims at correcting protein deficiency as they can be built up into the plasma and tissue proteins, thus maintaining an adequate nitrogen balance. In order to prevent amino-acids so given from being katabolised as a source of energy by being broken down in the liver into carbohydrates and nitrogen waste products, the addition of glucose and vitamins is necessary to provide the essential energy requirements of the body. Although intravenous infusions of plasma, so valuable in the treatment of shock, provide a ready source of plasma proteins, these must be broken down in the body before they can be reconstituted into tissue proteins. Therefore, when intravenous feeding has to be maintained for some time amino-acids, which are more readily utilisable, are to be preferred.

Certain amino-acids are essential and must be provided in the food proteins. These are leucine, isoleucine, lysine, methionine, phenylalanine, threonine, tryptophane, valine, histidine and arginine. The remaining amino-acids can be synthesised in the body from other amino-acids. This group includes glycine, alanine, proline, glutamic acid, tyrosine, cysteine, etc. Although it is possible to obtain the individual amino-acids and make up a suitable mixture of these, this procedure is very costly. The usual method of obtaining them is by means of the hydrolysis of proteins. Protein hydrolysates are usually prepared from casein, although blood, lactalbumen, meat, fish, soya and wheat have all been used. Hydrolysis can be effected by alkalis, acids or enzymes. Alkali hydrolysis results in racemisation and is not used. Acid hydrolysates are satisfactory, but tryptophane has to be added subsequently as it is destroyed in the process of hydrolysis. Enzymic hydrolysates generally produced by digesting casein with papein or pork pancreas does not destroy tryptophane, but care must be exercised to ensure the sterility of the product. Satisfactory preparations for intravenous use, which are free from pyrogenic and anaphylactic substances, are difficult to prepare at present and, therefore, such therapy is yet limited in this country, although there are commercial preparations available for oral and intravenous use.

Protein deficiencies are best dealt with by giving a high protein diet, provided that the patient is able to take this. Protein hydrolysates should only be used where the latter is not possible. The following conditions of protein depletion have been treated with protein hydrolysates when the patient has not been able to take a satisfactory diet: (1) **Where the patient is unable to ingest food proteins**; as in gastric and intestinal obstruction, particularly before and after operations; persistent vomiting, anorexia and peritonitis are other indications. Administration may be by intravenous drip or, in suitable cases, through a tube in the stomach. (2) **Where there is failure to digest and absorb food proteins**; as in severe gastro-enteritis and colitis and intestinal fistula. In infants they have been given for gastro-enteritis, cœliac disease and prematurity. They are also used in peptic ulcer, as they have a buffering action on the gastric juice. (3) **Where there is increased katabolism of body proteins;** as in burns, surgical and traumatic wounds, fractures, acute infections and toxæmias of pregnancy. (4) **Where there is increased loss of body proteins;** as in suppuration, burns, nephrosis and after hæmorrhage. (5) **Where there is deficient synthesis of body proteins in liver disease;** although it is doubtful to what extent protein hydrolysates benefit this group of cases. In this connection mention should be made of the protective function on the liver exercised by the sulphur-containing amino-acids, methionine and cysteine. Methionine is necessary for growth, for the formation of choline (*q.v.*) by virtue of its labile methyl groups and for the formation of cysteine because of its organic sulphur content. Whereas choline deficiency results in fatty infiltration and portal cirrhosis of the liver, cysteine deficiency causes massive necrosis of the liver and may lead to gross scarring and nodular hyperplasia. The administration of these amino-acids and choline in doses of 5 to 10 gm. daily to cases of liver damage is chiefly indicated where there is definite nutritional deficiency, and in cirrhosis when there is marked fatty infiltration and the pathological changes still reversible. Methionine has also been given to patients with exfoliative dermatitis and burns.

Methods of Administration of Protein Hydrolysates: *Oral preparations* are used where there is gross impairment of protein digestion. They may be swallowed in the ordinary way or given by gastric drip. Their taste is unpleasant and they require flavouring with black-currant juice, meat extracts or peppermint. *Casydrol Oral,** an enzymatic hydrolysate of fat-free milk, contains approximately equal parts of amino-acids (or polypeptides) and milk sugar. The average daily dose is 2 gm. per kilo body-weight, but this amount may be increased considerably in severe cases. *Parenteral preparations* must be previously tested experimentally *in vivo* for apyrogenicity. As mentioned above, they are indicated when oral feeding is impracticable. They are best given intravenously, but bone-marrow infusion has been used if this is impossible. They must be given slowly to avoid nausea and vomiting and to allow time for their metabolism. Some preparations contain dextrose, but others require this to be added. Vitamin supplements are necessary. *Casydrol Parenteral** is an enzyme digest of casein and meat proteins, and contains amino-acids (or polypeptides) 5%, dextrose 5%, sodium chloride ·3%, the preparation being isotonic with blood. It is advisable to give 50–100 gm. of dextrose about ½ hour before the infusion. The average daily dose of this preparation is about 1½ litres.

* * * * * *

Glycine (Aminoacetic Acid).

This substance influences creatine-creatinine metabolism in muscles and is used in *myasthenia gravis* and muscular dystrophies in doses of 15–30 gm. daily. In oral doses of 20 gm. daily, the drug can be given to improve blood supply in peripheral vascular diseases such as thrombo-angiitis obliterans.

Histidine hydrochloride, at one time administered by injection for peptic ulcer, is probably of little real value.

Successful fractionation of the plasma proteins has enabled valuable therapeutic agents to be evolved. Thus albumen, used as a 25% solution having the same viscosity but four times the osmotic concentration of plasma, can be used intravenously in conditions of hypoproteinæmia. γ globulin contains most of the antibodies of the blood, and preparations of it are now available for intramuscular injection for the prevention and treatment of measles. A coagulant present in the plasma globulins and absent in hæmophilia has been used to control hæmorrhage in this disease. The use of thrombin and fibrinogen as hæmostatics are referred to elsewhere.

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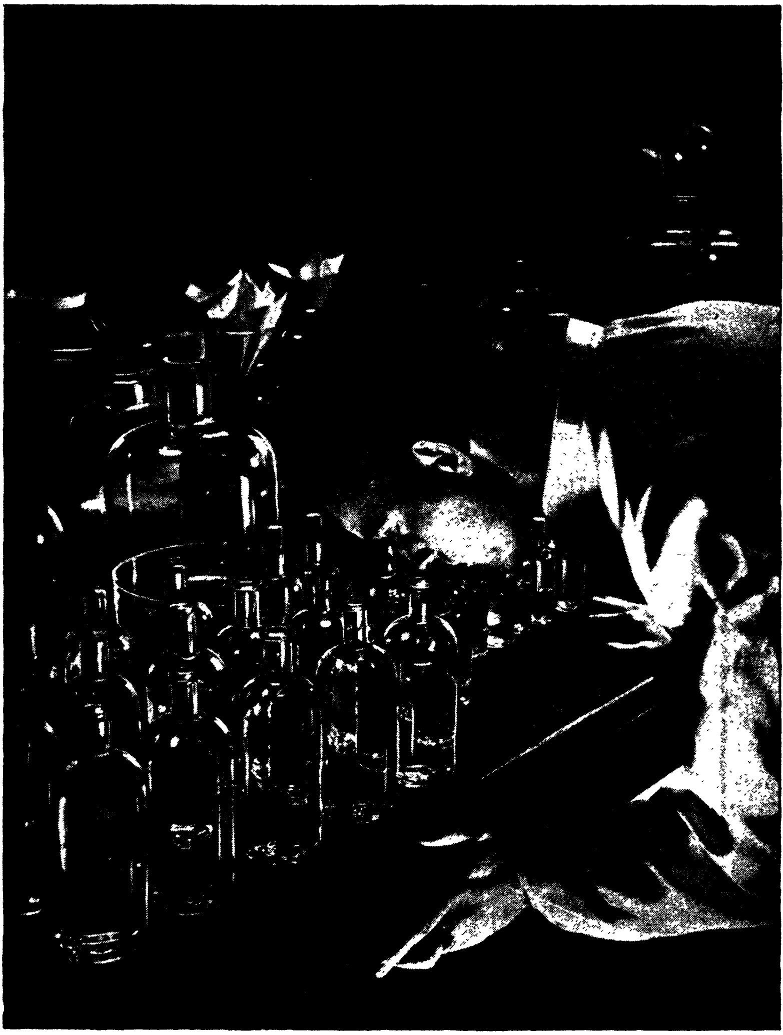

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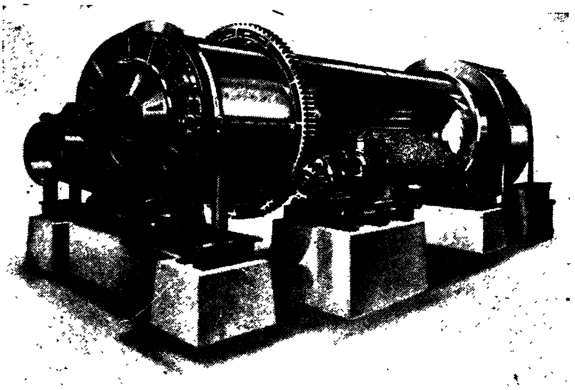

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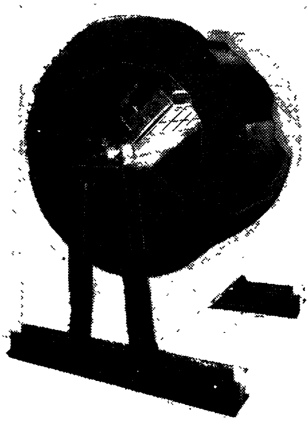

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